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ENDEMIC GOITER

The Adaptation of Man to Iodine Deficiency

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FOREWORD

An approach to the natural history of disease, perhaps not sufficiently employed, is the geographical, that is to say, the comparison of the pictures presented by certain maladies in one locality with those which they present in another. "Geomedicine," we may call it.

In the Thyroid Clinic of the Massachusetts General Hospital, for some years we had talked of the desirability of making geomedical studies of the diseases of the thyroid gland, but we had done nothing about it but talk until one day in the summer of 1950, when Dr. Hector Perinetti, of the Central Hospital in Mendoza, Argentina, did us the honor of paying us a visit.

Apropos of a patient with an enlarged thyroid shown in clinic that day, Dr. Perinetti took from his pocket a sheaf of photographs portraying patients of his own with some of the largest goiters that any of us, to that time, had beheld.

"Do you have many of these in Mendoza?" he was asked. "Yes, indeed. They abound all along the slopes of the Andes." "And has iodized salt not yet been used to wipe out this endemic?" "Yes, but not yet in Argentina," Dr. Perinetti replied, "but it soon will be introduced."

Thanks to the new methods of study recently introduced — radioactive iodine, antithyroid drugs, etc. — investigation of thyroid physiology, both normal and morbid, was in full swing at that time. Dr. Perinetti's display, therefore, provided the stimulus needed to convert a geomedical impulse into action.

The immediate consensus was to send an expedition to Argentina to study this goiter endemic by modern methods, and also to make it a joint enterprise of the United States and

Argentina, or more specifically of the Massachusetts General Hospital and the University of Cuyo in Mendoza and the Central Hospital there. The Andean Goiter Expedition was accomplished in the summer of 1951, and the present monograph is a full report of its findings. Preliminary reports have already been published.

The motivation must be made completely clear. It was purely one of scientific curiosity. No practical objective was envisaged. Endemic goiter has been abundantly proved to be due, in the final analysis, to shortage of iodine. Such features as naturally occurring goitrogenic substances may play a secondary role by diminishing the ability of the thyroid gland to collect iodine, but the disease fundamentally represents the result of the body's effort to maintain thyroid-hormone production in the face of a failing supply of iodine.

There is no practical problem — at least not a medical one — concerning endemic goiter because it has been known since the classic work of Marine and Kimball in 1917 that an endemic can be eliminated by providing the entire population of an endemic area with an adequate iodine intake. This can be largely accomplished by iodinizing table salt. On the therapeutic level, also, there is no problem because thyroid surgery in its present stage of perfection makes possible the safe and easy removal of endemic goiters already established.

The practical problems concerning endemic goiter, therefore, are not medical, but rather psychological, economic, or political. The problems, in other words, are those which are involved in the inauguration and conduct of goiter prophylaxis programs. Sir Charles Hercus of Dunedin, New Zealand, where they have a considerable endemic-goiter area, has told us that a difficulty was encountered when the government first tried to enforce the sale of iodized salt. The independent New Zealander felt that his rights were being invaded if he were forced to use iodized salt, even for

his own good. With sound psychological insight, however, the authorities got around this difficulty by providing both iodized and noniodized salt. If a customer does not expressly ask for noniodized salt, he gets iodized salt, and under these circumstances few persons ask for noniodized salt. A fairly effective prophylaxis program is under way in New Zealand, and everyone is happy about it.

The purpose then of the Andean Goiter Expedition was to take advantage of a unique opportunity to learn something of the physiology of the iodine-starved thyroid gland, not to discover new methods of controlling or treating endemic goiter. No on-the-spot studies by means of these new research instrumentalities had, to that time, been made on iodine-want goiter, and it seemed to the Boston group that the opportunity offered by Dr. Perinetti was not only unsurpassed for their purpose, but if not seized at once might cease to exist because, as stated earlier, the Argentine government was planning to start its goiter prophylaxis program.

As this report goes to press in 1954, we have learned that the sale of iodized salt has now been made mandatory in the Mendoza province. The research got finished just in the nick of time. The basic question asked by the investigators was, How does the thyroid safeguard hormone manufacture despite great difficulties in obtaining adequate amounts of the necessary raw material, iodine? The Mendoza situation was most favorable for the exploration of this question, and this new research, using the newly introduced tools of thyroid physiology, permitted the uncovering of certain new facts of iodine metabolism obtainable by no other method. Of course, many unanswered questions remain, but a beginning has been made, and it has been very gratifying that a permanent isotope laboratory has been established at Mendoza and a continuing research program inaugurated. In the final chapter of this report some indica-

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tions are given of the direction which further studies might take. The approach may have to be modified as the goiter prophylaxis program gets going. For some time to come, however, areas of uninhibited endemicity will doubtless remain in the Andes to which further expeditions can be sent for crucial data. Finally, it should be said that the scientific collaboration not only produced some new understanding of thyroid physiology, but on the human side it was instrumental in promoting international friendships among scientists, a cause most needing promotion in this unhappily divided world.

J. H. MEANS

PART I

INTRODUCTORY

Fig 1 The Republic of Argentina. The province of Mendoza and its capital city are shown in the diagonally hatched area.

1

THE MENDOZA ENDEMIC

The province of Mendoza is in the extreme west-central portion of Argentina near the Chilean border (Fig. 1). The capital city of the same name lies in the north-central part of the province, approximately 150 air miles from the Pacific Ocean and 600 miles from Buenos Aires near the Atlantic Coast. A few miles west of the city and forming the western portion of the province are the Andes, which in this region reach their highest point at Mount Aconcagua. This peak, towering 23,081 feet above the sea, is the highest in the Western Hemisphere. Other peaks nearly as high isolate the plains to the east from the rain clouds of nearby Chile, with the consequence that the province of Mendoza east of the Andes is arid. Of its 58,000 square miles, less than 1600 square miles, about a million acres, are under cultivation.

Mendoza derives its water from several streams which flow from the snows of the eastern slopes of the Andes. These streams have been drawn into irrigation projects since before the coming of the white man and have transformed the countryside into an agricultural region. The water that is not used locally escapes through the Desaguadero and the Tunuyán rivers, which later disappear into the deserts of La Pampa, never to reach the sea. The extensive irrigation systems supply water intermittently as needed for the vineyards, fruit orchards, and olive groves which form the principal industries of the province. During the night, water is admitted from reservoirs to flow through deep permanent

ditches along the streets of the city of Mendoza. Many inhabitants of the city use this water as their only supply.

The people consume a varied diet. Fruit grown locally is plentiful. Some meat is produced within the province, but because the arid lands are not suitable for extensive grazing a large fraction of the meat comes from nearer the sea to the eastward. Vegetables are produced locally. Most of the wheat comes from other provinces to the south and east. The enormous wine industry of the province contributes materially to the fluid consumption of the population. Water that is available for human use is hard; it contains an abundance of calcium and magnesium, but it is very poor in iodine.*

At the time of the census of 1940 the province of Mendoza had a population of 677,000, giving a population density of 1.17 inhabitants per square mile. Approximately 80 per cent of the inhabitants are native-born. The rest are chiefly Italians, Spanish, French, and English, with a few Germans, North Americans, Chileans, and Uruguayans. Very recently there has been a pronounced immigration from Italy to western Argentina. Few persons of Indian extraction are seen.

Goitrousness, which has always been common along the entire Andean chain, has long been characteristic of Mendoza. Among the earliest references to it is that of Don Nicolas de la Cruz y Bahamonde, who encountered in 1783 an innkeeper on the road from San Luis to Mendoza who was "originally from Malta, married and with three children who had, as well as all his family, goiter in the neck from drinking the rather salty water which runs in a nearby rivulet" [10]. In 1820 another traveler, a Mr. Peter Schmidmeyer, gained the impression that four-fifths of all the men and women of Mendoza had visible tumors of the neck [10].

* In the course of the present study, several analyses of Mendoza water were performed. Average iodine contents of three samples obtained from the municipal water supply were 2.1, 3.1, and 2.0 micrograms per liter. These are to be compared with 27.8 and 18.2 micrograms per liter for two samples of tap water in Boston.

Official attention was first paid to the problem when in the census of 1869 an attempt was made to enumerate goiter, cretinism, and deaf-mutism in the entire republic. At that time more patients with goiter were found in Mendoza than in any of the other Argentine provinces, and females outnumbered males by more than two to one. The disease was also found to be prevalent in the more northern provinces of western Argentina, especially Salta, Tucumán, and Jujuy. Goitrousness is now said to be more prevalent in these northern provinces than in the Mendoza area.

The usual variety of etiologic possibilities have been suggested to account for the Argentine endemic. Among these have been poverty [8], malaria [2], impurities in the water [1], excessive intake of calcium [5], arsenic [11], fluoride [5], and even intermarriage with Bolivians [2]. Many observers have stressed the relation between Chagas' disease and goiter and cretinism [3, 6]. Iodine-want was first seriously considered by Samuel Gache in 1895 [4], but was mentioned as only one among many possibilities. Iodine prophylaxis was introduced in 1924 by the National Department of Hygiene. The program was begun in Salta after a survey had shown that 90 per cent of schoolboys and 88 per cent of schoolgirls had goiter. The technique was to administer 0.5 gm of chocolate containing 2 mg of iodide to the school children at frequent intervals. Since then, iodine prophylaxis has been attempted intermittently in various provinces of the goiter belt.

In 1930 Mazzocco [7] published an extraordinarily thorough study of the relation of environmental iodine to goiter in Salta, a province north of Mendoza where the endemic problem is comparable. The concentrations of iodine in air, soil, water, and food and in the thyroid gland were compared with those which occurred in Buenos Aires. In each case it was found that iodine was less abundant in Salta. Several samples of soil from the environs of Buenos

Aires contained an average quantity of iodine which was ten times that of samples from Salta. Striking differences of lesser magnitude were found for foods and for water. The quantity of iodine in the glands of cattle from Salta was less than in cattle from a province on the Atlantic coast. The concentration of iodine per 100 gm of fresh gland was also less in the animals from Salta, and was inversely proportional to the weight of the glands.

Endemic goiter continues to be a problem in the province of Mendoza. In 1941 Perinetti and Freneau [9] described their findings in 52,548 school children between the ages of six and sixteen who were examined by a medical school board. Three categories of severity were used. The first included those glands which were palpable and enlarged but not visible. The second category included visible goiters, and the third included those that were distinctly nodular. Fifty-two per cent of the students were females, and 46 per cent of these were found to have goiter. Even if one discards the first category, 18.4 per cent of the female school children were found to be goitrous. Two per cent of all school children were found to have nodular goiter. In the 1940 military conscription it was found that of 3,360 recruits 426 had goiter. Of these goiters, 74.3 per cent were diffuse enlargements, and 22.2 per cent were nodular. The remaining 14 recruits with goiter (3.5 per cent) were considered to be hyperthyroid.

Today in Mendoza thyroid disease is one of the most common problems for which medical attention is sought. The majority of patients have nodular goiter, and of those requiring surgery almost all have nodular goiter. In 1950, among 1,117 patients with thyroid disease seeking medical help at the out-patient department of the Central Hospital of Mendoza, 33.8 per cent had diffuse enlargements of their glands, whereas 52.5 per cent had nodular goiter and another 5.2 per cent had nodular goiter with hyperthyroidism. Of those operated upon, 83.5 per cent had nodular goiter.

The Mendoza Patients

The Central Hospital of Mendoza is a large modern structure situated near the business center of the city. There are 600 beds available for in-patients. In addition, there is a large and active department for ambulatory care. Hospitalization is free, and occupancy of beds is at the discretion of the attending physicians.

The patients studied were largely selected from those attending the thyroid clinic of the hospital. One is shown in Fig. 2. Several of the studies which are described herein were conducted on patients who remained in the hospital, but the majority were done on subjects who lived at home. Observations were made on a total of 129 persons and on an additional nine at a later date. This latter group was used in a special investigation which is described in Chapter 6. The cretins described in Chapter 7 are not included in these groups.

Most of the 129 subjects were selected because they were in the younger age group and presented definite and obvious enlargement of their thyroid glands. For various reasons, a few patients with hyperthyroidism and hypothyroidism were observed. Limited observations were made on one patient with an hydatid cyst of the thyroid which was later removed. Three of the authors, D.S.R., G.L.B., and J.B.S., were included among the 129 subjects Because of the attention given to the enterprise in the daily newspapers, attendance at the goiter clinic of the hospital was overwhelming and an abundance of clinical material was available. Patient co-operation was unbelievably good. Many of the patients were requested to return daily to the laboratory for several weeks on end, including Sundays and national holidays, yet only three or four failed to keep their appointments.

With few exceptions, a history was taken and a physical examination was made of each patient. Historical data included the duration of enlargement of the gland, symptoms

deriving therefrom, family history of thyroid disease, history of medication for the goiter, and data regarding diet and water supply. The physical examination was directed primarily toward the thyroid gland itself, its configuration and size and such physical findings as might be related to altered function of the gland. A sample of blood for determination of the protein-bound iodine of the serum was drawn from each subject, and each received a tracer dose of radioactive iodide for 24- and 48-hour uptakes and excretion studies. In addition, certain patients were selected for the long-term observations described in later chapters.

It should be clearly understood that the patients chosen did not represent a cross section of the community at large. The study was directed toward investigating the metabolism of iodine in patients who were goitrous. The patients were selected with this in mind.

Clinical Studies

From the group of 129 persons who served as subjects for this study, adequate historical and physical data are available on 101 patients who were clinically euthyroid. The distribution of these patients by age and sex is shown in Table I.

TABLE I. DISTRIBUTION OF PATIENTS BY AGE AND SEX

Age (years)	Male	Female
10–19	9	15
20–29	5	23
30–39	9	22
40–49	2	11
50–59	—	2
60 on	—	3
Total	25	76

Twenty-five were male and 76 were female. Almost all were young. Only five were beyond the age of 50, and only eight-

Fig. 2 A typical patient with endemic goiter from Mendoza

een were 40 or more. No patients below the age of 10 were studied.

Almost all the patients were native to Mendoza or had lived most of their lives in the province. A few had lived near the sea for short periods of time. Seventy-six had spent their entire lifetime in western Argentina, and only two had lived there for less than 10 years. The exact duration of residence was unknown by 12, but was certainly in excess of one year.

The majority of patients had nodular goiter, and one had a thyroid gland of normal size. Only three of the 25 males had non-nodular goiter, whereas 17 out of 75 females had non-nodular goiter. In the age group from 10 to 19, the females were almost equally divided between those with non-nodular and with nodular goiter, but in the older age groups and in the male patients, nodular goiter predominated.

The duration of goiter in these patients is shown in Table II. As would be expected, the younger patients had

TABLE II. NUMBER AND DURATION OF GOITERS

Age (years)	Duration (years)				
	0–1	2–5	6–10	11 or more	Unknown
10–19	12	6	1	4	1
20–29	—	8	9	11	—
30–39	4	1	5	19	1
40–49	—	—	1	11	1
50–59	—	—	—	2	—
60 on	1	—	—	1	1

thyroid enlargement of relatively short duration. Of the 100 patients, 48 had had goiter for more than 10 years, and 64 for more than five years. An additional four patients did not know the duration.

There appeared to be a relation between nodularity and duration of goiter. Although 10 patients with nodular goiter

stated that the duration was no more than one year, in general nodularity increased with duration. Among the females, of 50 goiters of more than five years' duration, eight were non-nodular, and only one of the 14 goiters of similar duration in males was non-nodular. Forty-one out of 48 goiters of more than 10 years' duration were nodular. It must be emphasized, however, that the distinction between nodular and non-nodular goiter was purely a clinical one. Undoubtedly surgical removal of many of the non-nodular goiters would have disclosed nodularity that was not appreciated clinically.

In general, huge goiters were avoided in this study. The distribution by estimated weight of the thyroid gland is shown in Table III. The estimated thyroid weight for most

TABLE III. ESTIMATED WEIGHT OF GOITER.

Age (years)	Weight (gm)					
	0–24	25–49	50–99	100–199	200 or more	Not given
				Males		
10–19		2	2	3	—	2
20–29		—	3	2	—	—
30–39		2	2	3	2	—
40–49		—	—	1	—	1
				Females		
10–19	—	4	7	1	1	2
20–29	1	1	13	6	1	1
30–39	1	4	6	10	1	—
40–49	—	1	3	4	2	1
50–59	—	—	1	—	1	—
60 on	—	1	2	—	—	—

of the patients, male and female alike, fell between 50 and 200 gm and only 17 had glands that were less than 50 gm. It should be emphasized again that these estimates of thyroid weight were purely clinical approximations and as such were subject to considerable error.

There was a high incidence of a family history of goiter

among the patients who were studied. Sixty-four per cent had close relatives who had goiter, and many described several siblings, children, parents, and grandparents, who were goitrous. Thirty-two per cent gave no family history of goiter, and for 4 per cent there were no data. Four of our patients were mother-child pairs, and two others were siblings.

The casual and intermittent use of iodine-containing medications was very common in Mendoza. Many potential subjects for the study were rejected because of a recent history of ingestion of known or unknown drugs. Seventy-six of this group of 101 patients denied any medication containing iodine during the previous 12 months. No information regarding medication was available from an additional 12. Four had taken iodine within three months and 12 within a year. One had taken diiodotyrosine within three months and three within a year. None had taken thyroid within three months. Two had taken other iodine-containing drugs within three months, and seven had done so within a year. A few patients had taken more than one kind of medication.

Summary

1. Western Argentina is an endemic goiter area. Present information supports a lack of iodine as the principal etiological factor.

2. A laboratory for the study of patients with thyroid disease was established at the Central Hospital of Mendoza, Argentina. Facilities for the determination of radioactive iodine and for the chemical determination of iodine were installed.

3. The majority of patients were females of the younger age groups who had nodular goiters of an estimated weight of 50 to 200 gm.

4. Almost all of the patients were either native-born or

had lived in or near Mendoza for many years. Many had a family history of goiter.

5. Only 13 patients gave a history of recent ingestion of iodine or iodine-containing drugs.

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2

METHODS

The nature of the observations which were made on the Mendoza patients required that apparatus and techniques be devised which would permit measurements to be made rapidly and with satisfactory accuracy. It was necessary to assay the uptake and excretion of labeled iodide and the excretion of iodide, the concentration of protein-bound iodine in the sera, and on occasion the content of labeled iodine in the sera. The methods employed and their accuracy will now be described.

In Vivo *Measurements of Labeled Iodine**

The apparatus for *in vivo* measurements of radioiodine was simple in design. A bismuth-cathode Geiger-Mueller tube, shielded except in front by a lead housing with walls one inch thick, was placed on a high table with its open end facing the patient. Horizontal lead plates reaching from the upper and lower edges of the lead housing to the patient's neck provided a shielded compartment or box between the neck and the detector tube (Fig. 3). Pulses from the Geiger-

* The term "labeled iodine" will be met frequently in the text It refers to that quantity of iodine which was initially given to the patient as a tracer dose marked with radioactive iodine. *This quantity is independent of radioactive decay.* Thus the labeled [illegible]

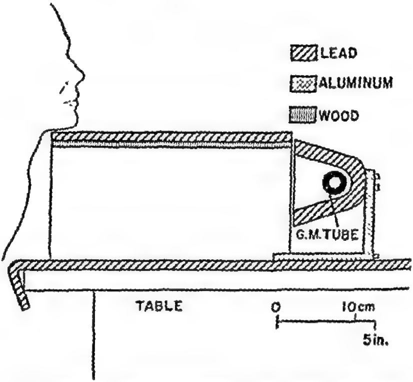


Fig 3 Diagram of apparatus used for *in vivo* thyroid measurements The bismuth-cathode Geiger-Mueller tube was mounted in a lead shield, and additional collimation was attained by lead plates placed on the surface of the table and on a wooden frame. The patient sat on a stool of adjustable height so that the chin rested comfortably on the upper lead plate.

Mueller tube were fed into a conventional scaler (Atomic Instrument Company Multiscaler). Measurements were routinely taken with a preset time of one minute, and three successive measurements were routinely made The background of the counter was approximately 100 counts per minute. The background counting rate was recorded several times each day.

The patient was seated on an adjustable stool in front of the counting array with his chin resting comfortably on the

upper surface of the upper lead plate. The patient was so placed that his thyroid was directly opposite the center of the counter tube. The position of the surface of the neck was adjusted by direct measurement to exactly 40 cm from the center of the tube, although the geometry of the apparatus was such that this position was usually achieved without adjustment. Measurements with known sources of radioactivity placed in the immediate area of the array but not directly in front of the open end indicated that shielding was excellent and that radioactivity from the rest of the body other than the neck was not appreciably detected. A myxedematous subject was studied to determine the contribution of radioactivity in extrathyroidal tissues. The maximum observed counting rate corresponded to 3 per cent of the administered dose in the "thyroid." This could well have resulted from the iodide in the blood and tissues of the neck and from radiation scattered from the rest of the body.

The large number of studies that were undertaken necessitated a simple and routine method for preparing individual tracer doses of radioactive iodide. Using the standardization furnished by Oak Ridge, a stock solution containing 100 microcuries per milliliter was prepared. Individual doses were obtained from this by taking 0.5, 1, or 2 ml and diluting to 100 ml in a 100-ml volumetric flask. The radioactivity of each tracer dose was measured before administration. The reference solution standard was made from 1 or 2 ml of the stock solution and the standard was used for all patients who received doses derived from that stock solution. Routine tracer doses were limited to 50 microcuries, but for special studies as much as 150 microcuries were administered to certain patients, and three patients who were studied immediately prior to thyroidectomy were given larger quantities.

Daily counting rates obtained with two of the standard solutions are shown in Fig. 4. These smooth curves indicate

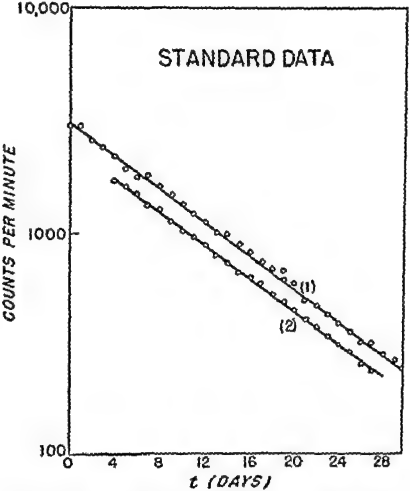


FIG. 4 Counting rates for two standards prepared on June 25 and June 29. The spread of the daily observations indicates that no gross changes in the counting apparatus occurred during the course of the experiments. The observed half-lives of I^{131} from the two curves are 7.86 and 8.00 days.

that there was no marked change in the sensitivity of the Geiger-Mueller tube. The half-times from the two curves were 7.86 and 8.00 days, in satisfactory agreement with the values of Sinclair and Halliday (8.04 ± 0.04 days) [7] and Lockett and Thomas (8.06 ± 0.02 days) [5]. It was interesting that with several patients, on whom measurements were made over a period of three weeks, the calculated thyroid-content data appeared to be smoother when the calculations were based on the smoothed standard curve than when the actual day-to-day standard values were used. This would seem to indicate that the daily error in the counting of the standard was greater than the daily variation in tube sensitivity. However, in either case the fluctuations resulting from variations in sensitivity or from changes in the counting rate of the standard were satisfactorily small. For convenience, the standard was measured at a distance of 37 cm from the center of the counter tube.

The counting rate recorded from a source of radioactivity is dependent in part upon the scatter of radiation from neighboring substances. In preliminary studies the counting rate of a 2-ml capsule containing a small quantity of radioactive iodide was found to be increased by 27 per cent when it was surrounded symmetrically with a beaker of water of 6.5-cm diameter. There was an increase of 23 per cent when a 9-cm diameter beaker was used, and of 29 per cent when a 10.5-cm beaker was used. If the beaker of 10.5 cm was adjusted so that the capsule was 2 cm behind the glass on the side nearest the counter, the increase in counting rate attributable to the presence of the beaker and the water that it contained reached a value of 45 per cent. In all cases the distance of the capsule from the counter tube was the same.

It was necessary to determine a factor that corrected for scattering and absorption as well as for inverse-square relations. This factor permitted comparison of counting rates obtained from the thyroid with counting rates obtained

from a known quantity of radioactive iodide in a 100-ml volumetric flask placed in the standard position. In this way, counting rates obtained from the neck could be referred to standard solutions, and percentage accumulations calculated. The actual determination of the factor was done in three ways following the methods of others [3, 4, 6], as follows.

Capsules containing 10 microcuries each of radioiodide were sewn into the two lobes of the thyroid of a cadaver. The cadaver was then placed before the counting array in the standard position. A net count of 6119 counts per minute was observed. The same quantity of radioactive iodide measured in a 100-ml volumetric flask and counted in the standard position gave 5196 counts per minute. The ratio of these two values is 0.849. For the second experiment, the same two small capsules containing radioactive iodide were placed adjacent to the surface of the neck at the level of the thyroid gland of a patient and held in place with adhesive tape. The counting rate observed was 6146 net counts per minute, yielding a factor of 0.845. In the water-phantom experiment, an increase of 45 per cent was observed when the source was surrounded by water in a manner similar to the tissue surrounding the thyroid. When a correction is made for the difference between the distance from the center of the standard to the Geiger-Mueller tube (37 cm) and the distance from the thyroid to the Geiger-Mueller tube (41 cm) a third value for the factor was obtained:

$$f = \frac{1}{1.45}\left(\frac{41}{37}\right)^2 = 0.85.$$

As a result of these observations, a factor of 0.85 was introduced in all *in vivo* measurements for uptake calculations. The recovery data tend to confirm the value chosen, since in only four out of the 117 patients did the sum of the labeled iodine in the thyroid and urine at 48 hours exceed 100 per cent.

Radioiodine Sample Measurements

The apparatus used for measuring radioiodine in the urine was similar to a Marinelli beaker. It consisted of a glass beaker with an inner concentric glass tube within which a bismuth-cathode Geiger-Mueller counter was placed. Urine was poured into the container to a predetermined volume of 800 ml. If this volume was not available or if a dilution was required because the sample was too "hot," an aliquot was taken and diluted to 800 ml. From a standard solution of I^{131}, 5 to 10 ml were removed daily for counting in the urine flask. This standard was identical with that employed in the *in vivo* counting. The urinary I^{131} excretion was determined by comparing the counting rate of the urine with that of the standard.

Because of the large number of samples that were measured with this apparatus, contamination, with consequent increase in background counting rates, proved to be an important consideration. The background counting rate was observed frequently each day, and whenever there was an appreciable increase a second unit was substituted to allow the first to be cleaned. Iodide was used liberally with the standard and urine samples to keep contamination at a minimum. Background of the urine counter was approximately 300 counts per minute and the sensitivity was approximately 1800 counts per minute per microcurie.

Plasma measurements of I^{131} were obtained by employing a dip counter constructed by the Radiation Counter Laboratories, following the design of Dr. A. K. Solomon of the Biophysical Laboratory of the Harvard Medical School. Four milliliters of plasma were used for each determination. The sensitivity of the tube was 41,000 counts per minute per microcurie and its background was 26 counts per minute. Plasma measurements were made only following large tracer doses of I^{131}.

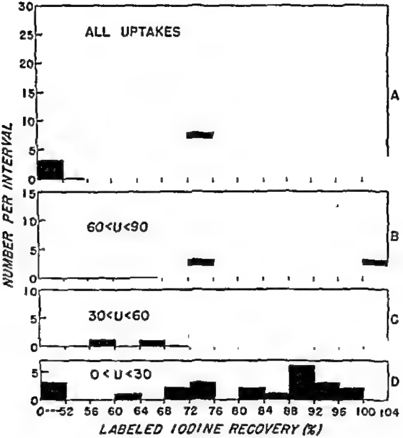
The Recovery of Labeled Iodine

Measurements of both uptake and total 48-hour urinary excretion of labeled iodine were available on 117 patients. Uptakes were measured at both 24 and 48 hours and the higher value was chosen as being nearer the theoretical uptake. The excretion is the total labeled iodine excreted in the urine during 48 hours. Recovery is defined as the sum of uptake and the 48-hour excretion. Figure 5(*a*) is a histogram of the recovery in all 117 patients. Only the initial determination on each patient has been included. Figures 5(*b*), (*c*), and (*d*) are similar histograms, but with the patients divided into subgroups with uptakes of 0–30 per cent, 30–60 per cent and 60–90 per cent respectively.

The average value of recovery in these patients has little meaning because of the straggling of data at low recoveries. The straggling undoubtedly arose chiefly from gross errors of urine collection. Straggling was more pronounced at low uptake values primarily because of the impossibility of having a recovery less than the uptake. However, it is interesting that all of the distributions seem to have a mode at approximately 92 per cent.

In addition to errors in urine collections, deviation of recovery from 100 per cent may arise either from errors of measurement, or because at the time of the *in vivo* measurement iodide had not yet been completely cleared from the iodide pool, or because an appreciable quantity of labeled organic iodine was in the extrathyroidal tissues when the uptake measurement was made. Error from incomplete clearance of iodide from the iodide pool would be confined to the low-uptake group. The amount of the labeled iodide in the iodide pool at 48 hours even in a patient with no uptake can be estimated to be no more than 3 per cent, assuming normal renal clearance.

One might expect that the amount of labeled hormone



[illegible]

and 30 per cent.

found in the extrathyroidal tissues at 48 hours would increase with increasing values of uptake. However, the data of Chapters 9 and 10 indicate that the amount of iodine in the thyroid and the rate at which labeled hormone is secreted are not well correlated with uptake. The average value of serum labeled iodine at 48 hours for the three patients of the

clearance study of Chapter 7 was 0.093 per cent per liter and, assuming a volume of distribution of 20 liters, the total quantity of labeled iodine in the extrathyroidal hormone pool was 1.86 per cent.

Incomplete urine collection is the most important factor which will produce a systematically low value for total recovery. Much of the spread of Fig. 5(*a*–*d*) is undoubtedly due to grossly incomplete urine collections. A large error in the uptake factor (0.85) would produce a deviation in recovery strongly dependent upon uptake.

It is difficult to assess the individual sources of error because of the many factors involved in the recovery measurement. However, the recovery data of Fig. 5 are consistent with the following:

1. A symmetrical distribution about the mode results from measurement errors or physiologic variations in the uptake factor;

2. The asymmetrical values below the mode result largely from incomplete urine collections;

3. The deviation of the mode from 100 per cent is in part due to the presence of labeled iodine in the iodide and extrathyroidal hormone compartments at the time the observations were made.

The Determination of Serum Protein-Bound Iodine

Sera for the determination of protein-bound iodine were stored frozen in tightly stoppered plastic tubes. Before removing aliquots for analysis the thawed serum was agitated in order to ensure proper distribution of the protein which tends to become concentrated in the lower part of the tube during freezing. The concentration of protein-bound iodine in each sample was determined in duplicate by the method of Barker [1] as modified by Carr *et al.* [2].

As an indication of the accuracy of this method, the agreement between duplicate analyses was studied statistically

using the data from the first control analysis for each patient. These control analyses of serum were available for all but two of the patients. However, in three instances there was not enough serum for analysis in duplicate, and in an additional two instances the duplicates agreed so poorly that the analyses were obviously inaccurate. For the remaining 119 analyses the mean difference between duplicates was $0.42\mu g$ per cent. The standard deviation of a single analysis was $\pm 0.39\mu g$ per cent, and the standard error of the mean of duplicate analyses was $\pm 0.28\mu g$ per cent.* Hence at a confidence level of 95 per cent, the true mean would be expected to lie within $\pm 0.6\mu g$ per cent of the observed value.

The Measurement of Iodide in Urine

Each patient whose uptake of radioactive iodine was studied collected his urine for at least two 24-hour periods immediately after the administration of a tracer dose. In the great majority of instances the two 24-hour urine specimens were analyzed separately, but a few analyses of pooled specimens were performed. Some of the 24-hour specimens of urine were analyzed chemically in Mendoza, but most of the analyses were done in Boston. Portions of the original specimens were stored under toluene at a temperature of 5° C. Although completion of the analyses required some eight months, there was no bacterial growth or change in volume during this period.

For the analysis of urine specimens the Carr [2] modification of the Barker [1] method was employed. All analyses were done in duplicate. The volume of urine analyzed was chosen so as to contain about $0.15\mu g$ of iodine. To insure

* Standard deviation $= \sqrt{\dfrac{\Sigma(\text{difference between duplicates})^2}{2\ (\text{number of differences})}}$;

Standard error of the mean of duplicate analyses $= \dfrac{\text{standard deviation}}{\sqrt{2}}$.

satisfactory recovery of the iodine present in the urine, 1 ml of a 15 per cent aqueous solution of hemoglobin was added to each sample and to each reagent blank before digestion. The necessity for adding such "carrier" protein has been noted by several previous investigators, and has been confirmed in the Boston laboratory.

As an additional check on the adequacy of recovery of iodine during the analytical procedure, a known quantity of carrier-free radioactive iodine was added to about one out of every five urines analyzed. This proved to be a most important safeguard against analytical error, since it soon became apparent that, for reasons unknown, the recovery of radioactive iodine, and hence of stable iodine as well, tended to decrease as the size of the aliquot of urine taken for analysis increased.* In order to compensate for the poor recoveries observed with large aliquots of urine, the mean recovery of radioactive iodine was plotted against the aliquot volume. From the curve so obtained, correction factors for each aliquot volume were calculated and used to correct all of the analytical values. These correction factors varied from about 1.06 for aliquots of 1 ml or less to about 1.47 for aliquots of 8 ml, the largest volume customarily used.

Two laboratories were engaged in the analysis of the urine specimens, one at the Massachusetts General Hospital, the other in the Pharmacology Department at the Harvard Medical School. Because of this, and particularly because the correction curve just described was slightly different in

* Since the larger aliquots of urine were likely to contain considerable quantities of chloride, and since chloride is oxidized to free chlorine and

for analysis.

the two laboratories, it seemed advisable to determine whether the results obtained in the two laboratories were in satisfactory agreement. This was done by subjecting a portion of the data to an analysis of variance. For a number of the patients the first 24-hour urine specimen had been analyzed in one laboratory, while the second had been analyzed in the other laboratory. With the patients arranged in alphabetical order so as to facilitate unbiased sampling, the first 14 whose original 24-hour urine specimen had been analyzed at the Massachusetts General Hospital were selected, and in similar fashion an equal number of patients whose first specimen had been analyzed at the Pharmacology Department were chosen. This technique of subsampling was employed in order to minimize any variation that might possibly be introduced by a tendency for a patient to collect 24-hour urine specimens more faithfully during the first experimental day than on subsequent days. Since each specimen was analyzed in duplicate, the 28 patients in this subsample contributed altogether 112 values for single analyses. In order to give more nearly equal weight to each individual chemical analysis and to each patient, the logarithm of the number of micrograms of iodine excreted per 24 hours rather than the daily excretion itself was used in the analysis of variance. The standard deviation calculated from the mean square for residual error with 56 degrees of freedom was ± 0.0473 log units. The corresponding standard error of the mean of duplicate analyses was about ± 8 per cent of the mean (± 0.0334 log units). The variance associated with differences between laboratories was not significantly greater than the variance for the error term ($P > 0.05$). This provided reasonable assurance that the results obtained in the two laboratories were indeed sufficiently comparable so that they could be pooled without further adjustment. While the variance for the interaction between laboratories and patients was highly significant ($P < 0.001$), this term was

necessarily confounded with the differences between 24-hour urine specimens collected by the same patient on successive days. Since the variance between laboratories was not significantly greater than the error variance, it seems probable that the large variance found for the interaction term was due chiefly to variations in the excretion of iodine by the same patient on different days rather than to any real interaction between laboratories and patients. This conclusion is substantiated by the similar variation of the results when urines collected by the same patient over a period of several days were analyzed in a single laboratory.

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3

PATHWAYS OF IODINE METABOLISM *

Iodine ingested with food and water is rapidly absorbed from the gastro-intestinal tract into the blood stream. While some absorption may occur from the stomach [11], the majority is absorbed by the intestine. If administered as free iodine or iodate, reduction to iodide is said to occur in the intestine before absorption takes place [7]. From the blood stream the iodide rapidly diffuses into the extracellular fluid of the tissues, its distribution for the most part being very similar to that of chloride [34]. Although largely excluded from most cells, the iodide ion freely traverses the red blood cell membrane. The concentration of iodide in the water of red blood cells is approximately equal to its concentration in the water of plasma, so that a given volume of red blood cells contains about 65 per cent as much iodide as an equal volume of plasma [18, 22, 24]. Distribution equilibrium between red blood cells and plasma is attained with great rapidity [18, 25].

In certain respects, however, the distribution of the iodide ion differs significantly from the distribution of the chloride ion, particularly when the concentration of iodide is small. The most obvious of these differences is the accumulation

* This chapter is taken with modification from a recent review by one of the authors (D S R [23]) The authors are grateful to the publishers of *Pharmacological Reviews* for permission to republish this material.

of the iodide ion in the thyroid gland. In addition, the concentration of iodide in salivary and gastric secretions far exceeds its concentration in extracellular fluid [16, 18]. The thirty-fold increase in concentration achieved by the salivary and gastric glands is of the same order of magnitude as the concentration gradient that can be maintained by the normal thyroid gland. As pointed out by Myant and his coworkers [18], the very high concentrations of iodide in saliva and gastric juice may account in part for the fact that the iodide ion has a larger volume of distribution than the chloride ion.

Although small quantities may be lost from the body in sweat and feces, the vast majority of the iodide in extracellular fluid eventually follows one of two pathways. It is either trapped by the thyroid gland to be manufactured into thyroid hormone, or excreted by the kidney. The thyroid gland and the kidney are therefore in competition with each other for the available supply of iodide. In the kidney the iodide is filtered through the glomeruli and is then partially reabsorbed by the tubules but to a far smaller extent than is chloride, at least in man.

Once trapped by the thyroid, iodide is rapidly converted to organic iodine by oxidation and combination with tyrosine. In successive reactions monoiodotyrosine and diiodotyrosine and then thyroxine are synthesized, and the completed hormone is pooled with the preformed hormone already stored in the gland as thyroglobulin. Under the controlling influence of the thyrotropic hormone of the anterior pituitary gland, the thyroid hormone is secreted into the blood stream in whatever amount is needed to maintain a reasonably constant plasma concentration. Although the thyroid hormone may leave the gland as free thyroxine [15], upon entering the blood stream it becomes rapidly, firmly, and almost completely bound to the plasma proteins. Several studies with butanol extraction and chromatographic separation have conclusively demonstrated that most of the

iodine bound to the plasma proteins is present as thyroxine [8, 14, 27, 32].

Unlike iodide, appreciable amounts of thyroxine do not enter the red blood cells [24]. However, protein-bound iodine, presumably thyroxine or a derivative of thyroxine, has been demonstrated within liver cells [5, 17] and probably exists within the cells of most, if not all, tissues. Gross and Pitt-Rivers [9] have suggested that 3,5,3′-*l*-triiodothyronine, rather than thyroxine, is the compound responsible for the calorigenic activity of the thyroid hormone. Presumably thyroxine is first converted to triiodothyronine and then, by reactions as yet unknown, is reduced to inorganic iodide which once again enters the general pool of iodide in extracellular fluid. There are thus two sources of iodide ion within the body: absorption from the gastro-intestinal tract, and breakdown of thyroid hormone in the tissues.

Although the majority of the hormonal iodine probably follows the pathway just described, a small portion may be removed from the blood stream by the liver and secreted with the bile into the intestine. Some of this may be reabsorbed, and the remainder lost to the body in the feces [29]. Finally, traces of thyroxine and diiodotyrosine have been demonstrated in the urine with chromatographic techniques.

In the following chapters a number of observations upon the metabolism of iodine will be described. In order that these may be expressed most clearly, it is helpful to introduce certain simplifying assumptions concerning the complex series of events that have now been described. Although simplification can be achieved without doing serious violence to the major facts of iodine metabolism, it should be clearly recognized that the resulting scheme will be to a certain extent abstract and artificial. The employment of a simplified model for a complicated biological system is warranted only if each assumption is explicitly stated and justified. We shall do this in the following paragraphs.

of the iodide ion in the thyroid gland. In addition, the concentration of iodide in salivary and gastric secretions far exceeds its concentration in extracellular fluid [16, 18]. The *thirty-fold increase in concentration achieved by the salivary* and gastric glands is of the same order of magnitude as the concentration gradient that can be maintained by the normal thyroid gland. As pointed out by Myant and his coworkers [18], the very high concentrations of iodide in saliva and gastric juice may account in part for the fact that the iodide ion has a larger volume of distribution than the chloride ion.

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tains all of the thyroid hormone outside of the thyroid gland, including any thyroxine that is undergoing enterohepatic circulation. It includes the organic iodine of the plasma and of the extravascular spaces with which the organic iodine of the plasma is in equilibrium.

Within each compartment the iodine is assumed to be uniformly distributed. If the actual concentration of iodine in one region of the body is relatively high, that region will represent a relatively large portion of the compartment. This may lead to occasional difficulties in interpretation. For example, Myant and his collaborators [18] have shown that after the administration of a tracer dose of labeled iodine its concentration in saliva or in gastric juice depends upon the concentration in plasma. However, there is a delay of approximately 30 minutes between the attainment of peak concentration in the plasma and peak concentration in the secretions of the alimentary tract. Fortunately, this delay in the attainment of equilibrium is not likely to interfere seriously with the interpretation of observations that extend over a period of more than an hour or two.

2 *Excretory Pathways.* While significant quantities of iodide may be lost in the sweat during profuse perspiration [28], this avenue of excretion is usually negligible and will not be considered in the discussions that follow. Moreover, iodide is so efficiently absorbed by the intestine that only minute traces of iodide ion escape from the body in the feces [12, 20]. Riggs [23] has reviewed the evidence for loss of iodine in expired air and has concluded that there is no appreciable excretion by this route.

Although traces of thyroxine may appear in the urine, the amount so excreted is probably negligible, at least in euthyroid subjects. It is assumed, therefore, that all of the iodine excreted in the urine is inorganic iodide.

In the following discussion it is sometimes assumed that fecal loss is negligible. In the rat a large fraction of injected

1. *Compartments.* It will be assumed that all of the iodine in the body is divided into three separate compartments. It should be obvious that these so-called compartments do not exist within the body as actual physical entities with clearly defined boundaries.

(*a*) Inorganic Iodide. This compartment contains all of the inorganic iodide in the body, including the iodide in the secretions of the alimentary tract, the iodide in red blood cells, and the iodide that is present in the thyroid gland and that has not yet been incorporated into protein. Although Oddie [21] has chosen to treat the inorganic iodide in the thyroid gland as a separate compartment, there seems to be no compelling reason to do so, since there is good evidence that iodide ions within the thyroid are freely exchangeable with the iodide ions in the blood stream. One practical difficulty does arise from inclusion of the iodide within the thyroid gland as a segment of the general iodide compartment. During studies with radioactive iodine, radiation emanating from iodide ions within the thyroid will necessarily be measured together with radiation from iodine that has already become organically bound. Some inorganic iodide may therefore erroneously be ascribed to the compartment of organic iodine in the thyroid gland. Usually the transformation of inorganic to organic iodine is so rapid that this error will be negligible. However, if conversion to organic iodine is blocked [2], due allowance must be made for the presence in the thyroid gland of a considerable amount of labeled iodide that properly belongs to the iodide compartment.

(*b*) Organic Iodine in the Thyroid Gland. To this compartment are assigned all of the organic compounds of iodine that occur in the thyroid. No distinction is made between iodine present as monoiodotyrosine, diiodotyrosine, triiodothyronine, thyroxine, or any unidentified compounds which may also be present [8, 26, 33].

(*c*) Extrathyroidal Organic Iodine. This compartment con-

gland are less active than the central follicles. Although no such anatomical separation of active and inactive follicles has been described in man, it is quite possible that there may be significant variations in the degree of activity from follicle to follicle. Furthermore, although iodide is swiftly oxidized and combined with tyrosine, conversion to thyroxine requires an appreciable period of time even in the rat, where the turnover of organic iodine in the thyroid gland is much more rapid than in man [6]. Finally, it might seem reasonable to suppose that newly manufactured hormone would be more available for immediate secretion than hormone previously synthesized and stored as colloid within the lumen of the follicles. This may indeed be true in certain patients (cf. Chapter 9). Despite these theoretical objections, several *studies of the rate of loss of labeled iodide from the thyroid* gland after the administration of a tracer dose have suggested that for periods of at least several weeks a reasonably constant fraction of the amount remaining in the thyroid gland is lost per unit time [4, 13, 30] This constant rate of loss suggests that the labeled organic iodine is fairly evenly distributed throughout the gland.

The rate of distribution of the thyroid hormone from plasma to the extravascular space is very much slower than the rate of distribution of the iodide ion [1, 19]. However, the bulk of unlabeled hormone already in the extrathyroidal compartment is so large compared with the quantity of labeled hormone secreted per day that the delay in distribution of radioactive iodine throughout the compartment of extrathyroidal organic iodine can be neglected. Accordingly, it will be assumed that the specific activity of hormonal iodine in the plasma is equal to the specific activity of hormonal iodine in all of the extrathyroidal spaces.

The simplified three-compartment model of iodine metabolism is shown in Fig. 6. In this figure the volume of each cube representing a compartment is proportional to the

thyroxine may appear in the feces. It seems probable that in man a much smaller fraction of the thyroid hormone escapes from the body by this route. Quantitative data on this point are meager. The fecal excretion of labeled iodine in eight patients given therapeutic doses of radioactive iodine for carcinoma of the thyroid was usually no more than 10 per cent of the daily urinary excretion of labeled iodide [29]. Fortunately, many of the calculations used in the present study did not require knowledge of the fecal excretion of iodine.

3. *Distribution of a Tracer Dose of Labeled Iodine.* The tracer doses of labeled iodine were administered by mouth to subjects in the postabsorptive state. When so given, absorption is quite rapid [31] Hamilton [10] found that absorption was 80 per cent complete within an hour. Keating and Albert [12] found absorption to be 90 per cent complete in 45 minutes and 99 per cent complete in 90 minutes. These figures indicate that when iodide is taken by mouth on an empty stomach there will be a brief but appreciable delay before absorption is complete. Time will also be required for the iodide to become evenly distributed throughout the iodide compartment. Brownell [3] estimates that 50 per cent of the final equilibrium concentration is attained in 15 minutes. At this rate 90 per cent of equilibrium would be reached in 50 minutes or 99 per cent in 100 minutes. In the discussion that follows, both the delay in absorption and the delay in distribution will be disregarded, and for the sake of simplicity it will be assumed that labeled iodine is instantaneously and evenly distributed throughout the iodide compartment.

It has been similarly assumed that when iodine enters either of the other two compartments it is rapidly and uniformly distributed. In the thyroid gland the validity of this assumption is somewhat dubious. It is well recognized that in the rat the thyroid follicles lying at the periphery of the

quantity of iodine contained by that compartment. The width of each arrow representing a pathway of iodine metabolism is proportional to the quantity of iodine which traverses that pathway per unit time.

4. *Equilibrium States and Iodine Balance.* Among endocrine organs the thyroid gland is unique in being not only a factory, but also a commodious storehouse for its hormone. This enables it to maintain a steady rate of secretion day after day, despite wide fluctuations in the quantity of iodide entering the body.

In the following chapters many of the deductions and conclusions will be based on the assumption that the experimental data were obtained from subjects in a state of iodine equilibrium, wherein the iodine intake balanced the loss of iodine from the body, and the quantity of iodide collected by the thyroid was equal to the quantity of iodine secreted as hormone. In fact, however, the thyroid gland is never in a steady state of equilibrium. Iodide intake is not evenly distributed throughout the 24 hours of the day, nor is it exactly the same from day to day. Because of the rapidity with which the iodide ion is collected by the thyroid gland and excreted by the kidneys, this irregular intake of iodine causes fluctuations from hour to hour in the blood concentration of the iodide ion, and corresponding variations in the absolute quantities of iodide collected by the thyroid gland and excreted by the kidney. Consequently, estimates of the total quantity of iodine handled daily by the body must be based upon analyses of 24-hour urine specimens or pools of such specimens.

It has been assumed that the excretion of iodine is equal to the dietary intake of iodine However, the existence of such a state of balance cannot be known with certainty. In any given individual, daily variations in iodide excretion will tend to cause errors in the estimate of *mean* iodine intake, but these errors will tend to cancel in a study of a large

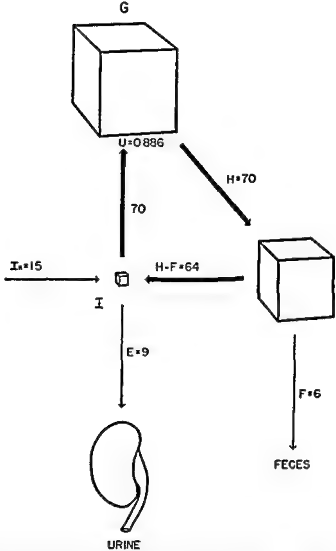

Fig. 6. A three-compartment model of iodine metabolism in a euthyroid subject after iodine balance has been attained in the face of a reduced intake of iodine. The volume of each cube is proportional to the amount of iodine in the compartment that it represents The width of each arrow is proportional to the number of micrograms of iodine traversing the

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number of individuals. On the other hand, it is possible that these patients were not even in long-term iodine balance. However, even if the patients were accumulating or losing iodine at an average rate of a milligram each year, the imbalance would be less than $3\mu g$ per day.

Summary

1. Present-day concepts of the metabolic pathways of iodide are described. The kidney and the thyroid gland are seen to be in competition for iodide which becomes available both from the diet and from the breakdown of thyroid hormone. Iodide that enters the thyroid gland is synthesized into hormone which in turn is secreted into the blood as organic iodine.

2. It is convenient to consider the various states of iodine in the body as "compartments." Thus, one may speak of *the iodide compartment, the organic iodine compartment of* the gland, and the organic iodine compartment of the blood and other extrathyroidal tissues.

3. The assumptions involved in a simplified model of *iodine metabolism are examined, especially those dealing* with the excretion of iodine, the distribution of tracer doses of labeled iodine, and states of iodine equilibrium and balance.

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PART II

FUNCTIONAL INTERRELATIONS

4

THE UPTAKE AND EXCRETION OF IODINE IN THE MENDOZA PATIENTS

In the course of study of the Mendoza patients, certain observations were made as a matter of routine. These included measurements of uptake of labeled iodine, of excretion of iodide and of labeled iodide, and of the serum concentration of protein-bound iodine. These data lend themselves to statistical treatment and in turn show certain interesting interrelations. Thus the frequency distribution of uptake and of hormone secretion rate can be charted, and the relations between uptake and iodide excretion and between uptake and serum protein-bound iodine can be shown.

The Uptake of Labeled Iodine by the Thyroid Gland

The uptake of labeled iodine by the thyroid gland was measured in 103 euthyroid subjects with endemic goiter before they were employed in any of the experimental studies. These control uptakes have been grouped in 5 per cent intervals and plotted as a frequency histogram in Fig. 7 Also in Fig. 7 is shown a normal frequency distribution of 48-hour uptakes in a region of iodine sufficiency constructed from the mean, 37.5 per cent, and standard deviation, ±10.1 per cent, reported by Skanse [4] for a group of 53 euthyroid subjects studied in Boston. The peak of the

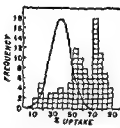

Fig 7. A frequency histogram of the control uptake of labeled iodine by the thyroid gland in 103 euthyroid subjects with endemic goiter Each square represents a single patient. The grouping intervals were from 0 to 4.9 per cent, 5 to 9 9 per cent, etc. The solid curve represents the normal distribution of uptakes in Boston calculated from the data of Skanse (see text).

Of the total group of 129 subjects, 11 were omitted because they were not euthyroid, 1 because she was taking iodine, 3 because the uptake was not determined, 7 because the serum protein-bound iodine was greater than 10 μg per cent, 1 because the analysis for serum protein-bound iodine was unsatisfactory, and 3 because they were euthyroid subjects studied in Boston and did not have endemic goiter.

curve was assigned an ordinate of 18, the modal frequency of the patients with endemic goiter. This curve has been calculated on the assumption that the frequency distribution is normal. Although it is improbable that any group of normal patients would follow precisely a normal curve of distribution, this curve serves to illustrate the differences between the uptakes of the two groups of patients.

The uptake of the Mendoza patients ranged from 11.2 per cent to 88.8 per cent, with a mean of 58.6 per cent ±1.94 per cent.* However, the distribution is obviously skewed to the left. The mode occurs at the 70 to 74.9 per cent interval. Well over half of the patients had uptakes greater than 57.7 per cent, Skanse's value for the mean plus twice the standard deviation for euthyroid subjects in Boston.

While it is obvious that the uptake tends to be high in patients with endemic goiter, it is equally clear that many of the subjects had uptakes within the range for euthyroid subjects living in a region of iodine sufficiency. The reason for this will become obvious from the relation between uptake and urinary excretion of iodide discussed in the following section.

The Urinary Excretion of Iodide and Its Relation to Uptake

From the discussion in Chapter 3 it is evident that all estimates of the amounts

* Standard error of the mean.

of iodine metabolized daily depend upon measurements of the excretion of iodide in the urine. If large day-to-day fluctuations in iodide intake, with correspondingly large variations in the daily excretion of iodide, occurred, it would be impossible to obtain satisfactory estimates of the mean daily excretion of iodide except by analyzing 24-hour urine specimens collected over a long period of time. Fortunately, in most of the patients studied in Mendoza the daily excretion of iodide varied within a satisfactorily narrow range.

The variation in iodide excretion from day to day was analyzed statistically in 25 euthyroid subjects who collected at least three consecutive 24-hour samples of urine during a control period. In this group the mean daily excretion of iodide was 23.6μg. The coefficient of variation (standard deviation expressed in per cent of the mean) varied from 13 per cent to 79 per cent, and had a mean of 39 per cent. These figures indicate that only very rarely would the true mean differ from the observed mean by more than a factor of two even when the mean was calculated from as few as three analyses of 24-hour urine specimens.

So long as iodine metabolism remains in the steady state, the daily secretion of hormonal iodine from the thyroid gland is related to the uptake and to the urinary excretion of iodide. The quantity of iodine entering the thyroid daily equals the quantity leaving, H, and also equals the amount of iodine entering the iodide pool multiplied by the uptake, U. Therefore

$$H = U(In + H - F), \tag{4.1}$$

where In is the daily oral intake of iodine and F is the daily loss in the feces. From the over-all balance of iodine, the following equation is obtained:

$$In = E + F, \tag{4.2}$$

where E is the quantity of iodine excreted daily in the urine. Substituting in Eq. (4.1) and solving for U, we obtain

$$U = \frac{H}{H + E}. \tag{4.3}$$

From this it is evident that, provided the rate of secretion of hormone from the thyroid gland remains reasonably constant, there is an inverse but nonlinear relation between the uptake and the excretion of iodide. Furthermore, as the excretion of iodide in the urine approaches zero, the uptake will approach unity as an asymptote, and conversely, as the excretion approaches infinity the uptake will approach zero as an asymptote.

Measurements of uptake of labeled iodide and excretion of iodide were obtained from 99 euthyroid subjects in Mendoza. These are shown in Fig. 8. The solid curve is a graph of Eq. (4.3) when a value of 57 is selected for H. This was the mean value of H calculated for 98 of the 99 patients. The observed points appear to follow the theoretical line fairly well, although there is considerable scatter. The flagrant discrepancies probably are due to patients who were far from equilibrium conditions. For example, as will be shown in Chapter 5, recent increase in dietary iodide may increase the excretion of iodide without immediate inhibition of uptake.

The implications of this relation are that the uptake of labeled iodide is dependent upon the iodide which is available to the patient, and that the "normal limits" of uptake for a population are dependent upon the iodide in the diet of the group.

Estimation of the Rate of Secretion of Thyroid Hormone

If Eq. (4.3) is solved for H, the result is

$$H = \frac{EU}{1 - U}. \tag{4.4}$$

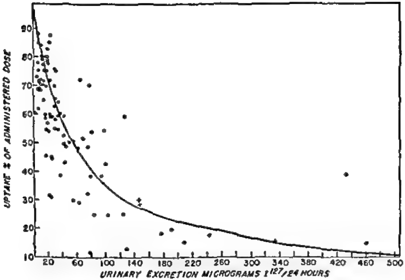

FIG 8. The relation between the uptake of labeled iodine by the thyroid gland and the mean daily excretion of iodide in euthyroid subjects. *Open circles represent patients studied in Mendoza whose mean iodide* excretion was calculated from analyses of only two 24-hour urine samples Solid circles represent patients studied in Mendoza whose mean iodide excretion was calculated from analyses of at least three 24-hour urine samples Crosses represent three of the authors studied in Boston One patient whose uptake was 58 per cent and whose mean excretion was 1000 μg per day was omitted from this graph.

The calculation of the curve is explained in the text. Of the total group of 129 subjects, 11 were omitted because they were not euthyroid, 2 because they were taking iodine, 7 because the serum protein-bound iodine was greater than 10 μg per cent, 9 because either uptake or excretion was not determined, and 1 because the analyses for iodide in the urine and for serum protein-bound iodine were unsatisfactory.

This equation has been used to calculate the rate of secretion of hormone for each of the 98 euthyroid patients corresponding to the points in Fig. 8. The frequency distribution of these individual estimates of the rate of hormone secretion is plotted in Fig. 9. In the group as a whole, the individual values range from 9 to 268 μg per day with a mean of 56.7 μg per day. In the subgroup of 27 patients whose mean rate of

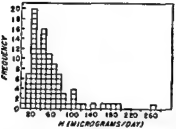

Fig. 9. Frequency distribution of rate of hormone secretion, H, of 99 euthyroid Mendoza patients as calculated by Eq (4.4).

urinary excretion of iodide was calculated from analyses of at least three 24-hour urine samples, the estimated rate of secretion of hormone ranged from 21 to 165 μg per day with a mean of 52.7 μg per day.

It is quite possible that in a region of iodine deficiency such as Mendoza the diet, though usually low in iodine, may occasionally be supplemented by the ingestion of considerable quantities of iodine derived either from special foods or from iodine-containing medication. If the urine specimens happened to be collected during one of these periods of elevated iodine intake, the corresponding estimate of the rate of hormone secretion would be unusually high. This may well account for the skewing of the frequency distribution seen in Fig. 9.

The hormone secretion H may be calculated for an individual or from studies of a considerable number of euthyroid individuals. For the latter purpose, a logarithmic transformation of Eq. (4.4) is useful:

$$\log E = \log H + \log\left(\frac{1}{U} - 1\right). \tag{4.5}$$

According to this equation, a graph of log E against $\log[(1/U) - 1]$ should give a straight line with a slope of unity, and the intercept of this line with the zero axis for $\log[(1/U) - 1]$ should provide an estimate of log H. Data for the 99 euthyroid subjects have been plotted in Fig. 10 according to this transformation.

It would be desirable to estimate log H by calculating the best straight line determined by the scatter of points, but the usual technique of calculation by the method of least

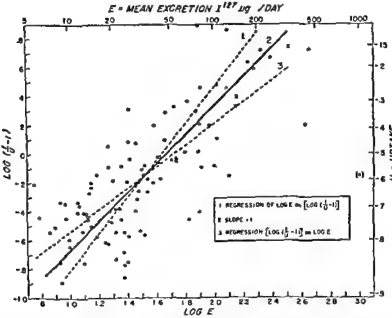

Fig 10. The relation between the logarithm of the mean daily excretion of iodide and the logarithm of $[(1/U) - 1]$ in the 99 euthyroid subjects of Fig 9 Open circles represent patients studied in Mendoza whose mean iodide excretion was calculated from analyses of only two 24-hour urine samples Solid circles represent patients studied in Mendoza whose mean iodide excretion was calculated from analyses of at least three 24-hour urine samples Crosses represent three of the authors studied in Boston. The open circle in parentheses has been omitted from the calculations The calculation of the two broken regression lines and of the intermediate solid line is discussed in the text The coefficient of correlation between the two variables is 0.77 The slopes of the regression lines are highly significant, t for 96 degrees of freedom being 11 8.

squares [5] is not entirely satisfactory for these data. Except for the selection of the kind of patient studied, the values obtained for uptake were not in any way deliberately selected by the investigator. They are therefore subject to random errors of sampling. The same holds true for the daily excretion of iodide. In addition, both variables are influenced by errors of measurement. Furthermore, since neither log E

nor $\log[(1/U) - 1]$ is an independent variable, the method of least squares could be used with as much justification for the calculation of the regression of $\log E$ on $\log[(1/U) - 1]$ as for the calculation of the regression of $\log[(1/U) - 1]$ on $\log E$. However, as Berkson [1] has pointed out, each of the regression lines so obtained represents a biased estimate of the true relation between the two variables, and the best straight line representing the true relation cannot easily be calculated from the observed data. However, the two regressions shown as broken lines in Fig. 10 are biased in opposite directions. The best estimate of the true relation lies somewhere between the two, and passes through their point of intersection whose coordinates are the means of the abscissal and ordinal values. The solid line in Fig. 10 has been drawn through this point and has been given a slope of unity, the theoretical slope defined by Eq. (4.4). It is evident from the figure that the theoretical line does lie between the two lines of regression and, indeed, very nearly bisects the angle formed by them. This provides some assurance that the observed points actually obey the relation predicted by the equation. The intercept of the solid line on the zero axis for $\log[(1/U) - 1]$ is 1.67, which corresponds to a mean rate of secretion of 46.5 μg of hormonal iodine per day. This value of H is slightly lower than the mean of the individual calculations of H, but the latter falls within the two regression lines of Fig. 10.

Because the frequency distribution of H calculated for each patient individually (Fig. 9) is skewed to the right, the mean value of H calculated from the logarithmic transformation will necessarily be lower than the arithmetical mean of the individual values. Since there is good reason to give the high individual values their full weight, the arithmetical mean is the better estimate of the average value of H in this group of patients.

Calculation of the rate of hormone secretion according

to the methods outlined above depends upon several assumptions, none of which holds strictly true for the actual experimental conditions The calculated value of hormone secretion will be in error to the extent that the assumptions are not valid. These sources of error will now be reviewed.

1. *Incomplete Collection of Urine.* The validity of the calculations obviously depends upon obtaining accurate measurements of the urinary excretion of iodide in complete 24-hour urine samples. It is improbable that all of the urine collections were actually complete. This problem has already been discussed in Chapter 2.

2. *Discrepancies Between the Observed Uptake and the Theoretical Uptake.* The theoretical uptake, U, is the fraction of a tracer dose of labeled iodide that would be accumulated by the thyroid in infinite time if there were no secretion of labeled hormone from the gland. However, it is impossible to measure the theoretical uptake because loss of labeled hormone may occur before collection of the administered labeled iodide is complete. The error in the measurement of U, therefore, is in the direction of underestimating it, especially in those patients with small quantities of iodine in their glands (cf. Chapter 9). However, there appears to be no tendency for the points of Fig. 10 to cluster above the lower portion of the theoretical line. This fact suggests that the error introduced by the discrepancy between the observed and the theoretical uptake is not sufficiently large to bias the calculations based upon the observed uptake.

3. *Departures from the Steady State.* The subjects selected for study in Mendoza may have been in iodine imbalance. What is actually calculated is the rate at which iodide is being collected by the thyroid gland, and only in the steady state can this legitimately be equated to the rate of secretion of hormonal iodine. If there were any tendency toward a positive or negative iodine balance, the actual rate of secretion would be less or larger than the rate of collection, and

Eq. (4.4) would, therefore, give an overestimate or underestimate of the true rate of thyroid hormone secretion.

Despite these three sources of error, the figure of 57 μg per day is probably not far from the true secretion rate, and since the first two sources of error would tend to produce a systematically low value of H, the true rate is probably slightly higher. The daily rate of secretion calculated from the maintenance requirement for exogenous hormone by patients with complete myxedema is about 90 μg [3]. This is probably an overestimate of the true hormone requirement, since it is unlikely that exogenous hormone is utilized with complete efficiency.

The mean value of H calculated above applies only to these patients, and is not necessarily valid for all populations whose members appear to be clinically euthyroid. One might expect that, in patients with endemic goiter, the rate of secretion of thyroid hormone, and correspondingly the blood concentration of hormone, would on the average be somewhat lower than in regions of iodine sufficiency. However, it is not known how much of a decrease in plasma concentration of hormone is needed to maintain stimulation of the anterior pituitary gland. Most of the patients studied in Mendoza were not only clinically euthyroid but also had serum concentrations of protein-bound iodine that were well within the normal range. This suggests that a clinically or chemically detectable degree of hypothyroidism is not required for maintenance of thyroid hyperplasia in the face of iodine deficiency.

Serum Protein-bound Iodine and Its Relation to Uptake

Satisfactory control determinations of the concentration of protein-bound iodine in the serum were available for most of the 114 euthyroid subjects studied in Mendoza. In two instances a blood sample was not obtained, and in two additional instances agreement between duplicates was

unsatisfactory. The values obtained in the remaining 110 subjects ranged from 2.1 μg per cent to 63 μg per cent. However, of six patients whose protein-bound iodine exceeded 10 μg per cent one was taking diiodotyrosine, one was taking iodobismuthate of quinine, and two had had some form of iodine-containing medication within the previous year. Although the remaining two subjects gave no definite history of having taken any iodine supplements, the urinary excretion of iodide was 150 μg per day for one and 318 μg per day for the other. These values are high for Mendoza and suggest that the elevated concentrations of protein-bound iodine may have been due to exogenous iodine. It was, therefore, decided to omit these six determinations from further consideration.

In the remaining group of 104 subjects, the mean concentration of protein-bound iodine was 5.81 μg per cent with a standard deviation of ± 1.81 μg per cent and a standard error of the mean of ± 0.17 μg per cent. These values indicate that the "normal" range of protein-bound iodine in the euthyroid subjects with endemic goiter was 2.2 to 9.4 μg per cent (mean plus or minus twice the standard deviation). This range is somewhat broader than the range usually considered normal in regions where the supply of iodide is adequate. For example, Kydd, Man, and Peters [2] found that the protein-bound iodine in 80 normal subjects ranged from 3.8 to 8.6 μg per cent with a mean of 5.4 and a standard deviation of ± 0.94 μg per cent. While the difference between their mean and the mean for the Mendoza subjects is not quite significant statistically (*P* slightly > 0.05) the greater variation among the Mendoza subjects is evident from the almost twofold greater standard deviation. In the group of 104 euthyroid subjects with endemic goiter, the protein-bound iodine was less than 3.0 μg per cent in 3 patients and greater than 8.0 μg per cent in 13 patients. However, 85 per cent of the values lay within the range of 3.0 to 8 0 μg per cent.

There was a significant correlation between the protein-bound iodine and the uptake of labeled iodine. Despite the wide scatter of points, the slope of the regression line was highly significant, t for 99 degrees of freedom being 4.79 [5]. The coefficient of correlation [5] was −0.43. Low concentrations of protein-bound iodine tended to occur in patients with high uptakes, perhaps because the thyroid gland was not able to compensate fully for an extreme reduction in iodine supply. On the other hand, patients with a high concentration of protein-bound iodine tended to have relatively low uptakes. This may indicate that these patients were receiving iodine supplements, perhaps in the form of organic compounds of iodine, which would simultaneously elevate the protein-bound iodine and reduce the need for a high uptake of iodide by the thyroid gland.

Summary

1. The uptake of labeled iodine by the Mendoza patients was higher than for patients from a nonendemic district.

2. There was an inverse correlation between the uptake and the urinary excretion of iodine. Thus, the uptake is dependent upon the iodine that is available to the patient in his diet.

3. The secretion rate of thyroid hormonal iodine was calculated for 98 euthyroid Mendoza subjects. The mean was 56.7 μg per day when the calculations were made for individual subjects, and 46.5 μg per day when the rate was calculated by a graphical method described in the text.

4 The mean concentration of protein-bound iodine in the serum was scarcely different from the mean normal value obtained from an area of iodide abundance, but the spread of values was wider.

5. There was a significant inverse correlation between the serum protein-bound iodine and the uptake.

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5

THE EFFECTS OF SUPPLEMENTARY IODIDE ON THE RETENTION OF IODINE

This chapter is concerned with the administration of supplements of iodide to patients with manifest iodine deficiency. The study was divided into two parts. In the first, iodide was given to each patient in a small daily dose for several weeks. In the second, iodide in varying amounts was administered in a single dose simultaneously with a tracer dose of labeled iodine. In both studies the effects of the iodide on the uptake and excretion of both iodide and labeled iodine were observed.

Daily Iodide Supplements

Thirteen persons who had palpable enlargements of their thyroid glands and elevated uptakes of labeled iodine were selected. Each was given a daily ration of potassium iodide either in liquid form, or, in the latter weeks of observations, incorporated in a soft and readily soluble pill. The subjects lived and ate at home. Uptake studies were made weekly for the first several weeks and less frequently thereafter. The subjects were divided into three groups for various dose schedules.

Group I: 150 μg of iodide daily. The seven patients of this group had a mean initial labeled iodine uptake of 71 per

cent with a range from 61.3 per cent to 85 per cent. The mean initial 24-hour excretion of iodine calculated from an average of two successive 24-hour urine specimens for each subject was 12.3 μg, with a range from 5.7 to 33.8. The uptakes for each individual are plotted against time in Fig. 11. It can be seen that in five patients the uptakes fell slowly, whereas in two there was a more rapid fall. The mean uptakes for the seven subjects are plotted in Fig. 12. The individual determinations contributing to each point were made within two days of the times as shown. The final average uptake was 53 per cent, a fall of 18 per cent in 50.1 days. The patient of the lowest curve had reached a normal uptake by the twenty-eighth day and was not studied further. For purposes of calculating the final points of the curves of Fig. 12, the uptake and excretion values for this patient are assumed to have been unchanged after the twenty-eighth day. Excluding the iodide of the diet, the mean intake of iodide during the 50.1 days of observation was 7515 μg for each patient.

Estimates of the net gain (positive balance) of iodine have been made in two ways. If it is assumed that the control average 24-hour excretion of iodide in the urine, E_0, equaled the average daily iodide in the patient's own food and drink for the duration of the experiment, then this plus the 150 μg daily supplement, S, is the daily intake (150 + 12.3 = 162.3 μg). It is plotted downward from the base line in the upper portion of Fig. 12. Neglecting fecal excretion, the area of the rectangle, therefore, represents the total iodide intake during the 50.1 days of observation. The quantity of the intake that was retained is estimated either by plotting upward from the intake line the mean daily iodine excretion calculated from two 24-hour urine samples (solid line), or by plotting downward from the base line the product of the intake of iodide ($E_0 + S$) and the fractional uptake of labeled iodine, U, for that day (dashed line). The first of these methods is dependent upon the urinary excretion of iodide;

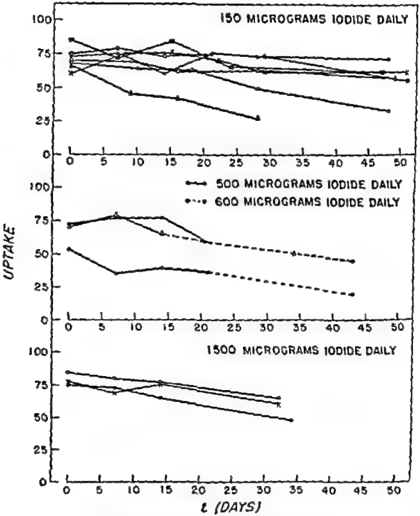


Fig. 11. The changes in uptake in groups of patients given varying daily doses of supplementary iodide. The abscissa is time in days; the ordinate is percentage of the accumulated dose in the thyroid gland after 24 or 48 hours, whichever was the higher. The dose schedules of iodide are indicated

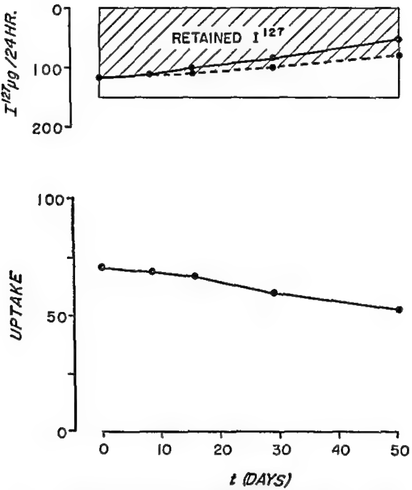


FIG. 12 The average decline in uptake and the balance of iodide in seven patients who received 150 μg of iodide daily. The total daily intake of iodide, $(E_0 + S)$, is plotted downward from the zero line in the rectangle above. The solid line is the retention of iodide estimated from urinary excretion. The broken line is the retention of iodide estimated from labeled iodide uptake.

the second is independent of urine collections during the experimental period, and is dependent upon *in vivo* measurements. Fecal loss is assumed to be constant. The initial point of both balance curves was calculated by the second method since iodine-excretion data were not available for locating the initial point of the curve by the first method. The agreement between the curves calculated by the two methods suggests that urine collections were reasonably accurate.

The curve that is based on uptake data should have a slight upward correction to account for the urinary iodide which is derived from the peripheral breakdown of thyroid hormone. The theoretical iodine retention as shown in Fig. 12 is calculated to be $U(E_0 + S)$. Actually, there should be subtracted from this the iodide that derives from the breakdown of hormone and is lost in the urine. Its value is $H(1 - U)$, where H is the quantity of hormonal iodine secreted daily. This latter term is low for high values of U, and is of relatively little consequence when the intake of iodide is large. it becomes of increasing relative importance as the uptake falls and iodide equilibrium is approached. It has been neglected because the value of H cannot be precisely known in these patients whose gland content of hormonal iodine was changing. Were one to assume a value of 57 μg per day for H, the two curves of Fig. 12 would be very nearly superimposable. In subsequent balance curves the iodine intake was so high that neglect of H no longer introduces appreciable error.

From Fig. 12 it appears that supplementation of the diet of the deficient subject with a daily ration of 150 μg of iodide is attended by a gradual approach to a new iodide balance. The time necessary for balance to be regained can only be approximated from these data. Assuming that the approach to the new equilibrium proceeded at the steady rate illustrated by the solid line of Fig. 12, balance would

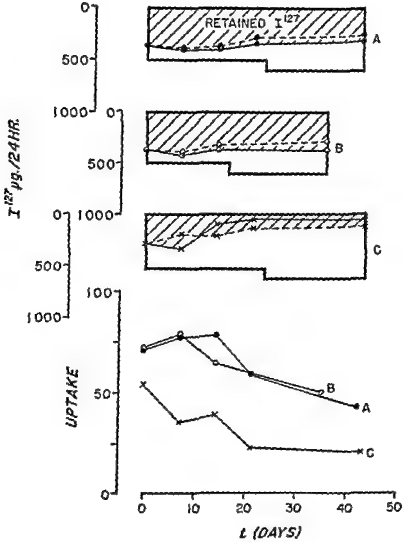
have been restored on day 99.3. At that time there would have been a net accumulation of 5.82 mg of iodine in the gland. This is of the order of magnitude of the iodine content of the normal thyroid, although obviously it is only an approximation.

For reasons that are not clear, one of these patients showed a more rapid rate of fall of labeled iodine uptake than did the others. Although the initial uptake was high (68 per cent) and the iodide excretion low (9.8 μg), the uptake on the twenty-eighth day was 27.9 per cent, and the iodine excretion was 152 μg. This gives a net positive balance of only 7.8 μg per day on the twenty-eighth day. The balance calculated on the basis of uptake, and assuming a hormone output corresponding to 57 μg of iodine daily, was 3.6 μg per day. Thus equilibrium was practically achieved in this patient within four weeks during which a total of 1.31 mg of iodine was retained.

A theoretical objection to the methods of estimating balance which have been employed is that the frequent tracer doses of radioactive iodine may have caused a functional impairment of the gland. This seems improbable. Not only were doses of less than 50 microcuries employed, but the retained radioactive material was distributed throughout glands that were several times normal size. The maximum total dose given to any one of these patients was less than 300 microcuries.

Group II: 500–600 μg of iodide daily. This group comprised three patients. For the first two or three weeks each received 500 μg daily of iodide. Thereafter the dose was increased to 600 μg when 150 μg tablets of iodide became available. One of the subjects had a control uptake that was only slightly above 50 per cent. The data are illustrated in Figs. 11 and 13.

This daily dose of iodine resulted in a progressive fall in the uptake of labeled iodine. The fall appeared to be some-


RETAINED I^{127}
A
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what more rapid in the patient who began the study with the lowest uptake. There was a tendency toward restoration of iodide equilibrium (Fig. 13), although this was striking only in patient C. While the increase in supplement from 500 to 600 μg was accompanied in patients A and B by a further fall in uptake, this was hardly more than enough to compensate for the increased iodide intake, and the balances were scarcely changed.

By whatever method it was calculated, whether by subtracting the iodide excretion from the sum of the control iodide excretion and the daily supplement, or by calculation from the uptake as already described in the previous section, there was a surprisingly large positive balance of iodine. At the end of forty-two days patient A had already retained at least 12.5 mg of iodine, and was retaining iodine on that day at a rate of 252 μg per day. Patient B had retained at least 11 mg by the thirty-fifth day and was on that day continuing to retain iodide at a rate of 278 μg daily Patient C, who began the experiment with an uptake of only 54.2 per cent, approached equilibrium much more rapidly and had nearly attained it by the end of three weeks.

The initial control serum protein-bound iodine values were 4.3 and 6.6 μg per cent for A and B respectively, and at the conclusion of the observations these were 3.6 and 6.2 μg per cent. The initial protein-bound iodine of patient C was 4.3 μg per cent and at the conclusion of the experiment was 5 2 μg per cent.

Group III: 1500 μg of iodide daily. There were three patients in this group The average control uptake was 79.2 per cent, with a range from 75.6 to 84.6 per cent. The mean control 24-hour iodine excretion was 11.5 μg, with a range from 7 4 to 14.3. The final average uptake of labeled iodine was 57.9 per cent. The data are shown in Figs. 11 and 14 and Table IV. There was a steady fall in the uptake as the daily dose of iodine was continued, and there was also an evident

TABLE IV. UPTAKE, IODIDE EXCRETION, AND SERUM PROTEIN-BOUND IODINE DURING THE ADMINISTRATION OF 1500 μg OF IODIDE DAILY.

	Patient A			Patient B			Patient C		
Time (days)	Labeled-iodine uptake (per cent)	Iodine excretion (μg/24 hr)	Serum protein-bound iodine (μg/100 ml)	Labeled-iodine uptake (per cent)	Iodine excretion (μg/24 hr)	Serum protein-bound iodine (μg/100 ml)	Labeled-iodine uptake (per cent)	Iodine excretion (μg/24 hr)	Serum protein-bound iodine (μg/100 ml)
0	75.6	14.3	4.8	84.6	12.8	2.3	77.4	7.4	3.1
7	72.7	318	4.6	79.6	91.7	4.7	68.8	31.1	9.4
14	58.5	390	—	76.5	148	3.9	75.0	60.6	15.5
33	41.0	626	5.8	64.6	386	4.9	56.4	307	13.6

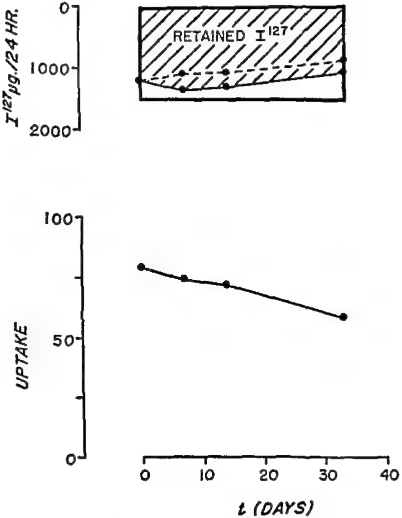

Fig. 14 The fall in uptake of labeled iodide and the retention of iodide in 3 patients who received 1500 µg of iodide daily. The construction of the chart is identical with that of Fig. 12.

but moderate tendency toward restoration of iodine equilibrium during the thirty-three days of observation.

In this group there was a much larger positive balance of iodine. During the thirty-three days of observation, the net positive balance was 34.1 mg, and on the thirty-third day the retention rate was 874 μg per day. In these approximations the term $H(1 - U)$, which would have been small, has been neglected for reasons already given. If this rate of approach to equilibrium had been maintained, it can be estimated that the net positive balance at equilibrium would have been 72 4 mg of iodine, and would have been reached in 121 days. These estimates are purely speculative, however, for at least one of the three subjects, instead of approaching a state of balance, developed thyrotoxicosis.

The patient who developed thyrotoxicosis was a 46-year-old married female who had immigrated to Mendoza from Italy at three months of age. She had two children. She had been aware of an enlargement of her neck for at least eight years, and during the past year the mass had grown more rapidly. She had no symptoms that were suggestive of hyper- or hypothyroidism. The physical examination was not remarkable except for a firm, elastic multinodular thyroid gland which had an estimated weight of 150 gm. The pulse was 72. After thirty-three days of daily doses of 1500 μg of iodide as potassium iodide, the protein-bound iodine was 13.6 μg per cent (Table IV). After seventy-eight days the patient presented the classic signs of thyrotoxicosis, including asthenia, tremor, tachycardia, excessive sweating, and weight loss. The basal metabolic rate was found to be +84. Her thyrotoxicosis was subsequently controlled with methylthiouracil.

Discussion. The slow approach to new equilibrium states exhibited by these three groups of patients illustrates the remarkable capacity of the thyroid gland to adapt itself to wide fluctuations in iodine supply. The iodine-deficient gland

responds to an improved supply of iodine by storing it away against possible future needs. The throttling down of the high uptakes proceeds so slowly that the glands can be filled with stored hormone. Indeed, the processes of hormone synthesis appeared to overshoot the needs of the body when the iodide supply was in excess of normal.

The development of thyrotoxicosis in the patient of Group III is reminiscent of reports that the use of iodine supplements in patients in areas of endemic goiter is accompanied by a rise in the incidence of hyperthyroidism, and that the administration of iodine to patients with adenomatous goiter, especially those in the older age group, may cause the appearance of thyrotoxicosis, or accentuate it if it is already present. This possibility was clearly described by Rilliet in 1860 [14] and later by Breuer in 1900 [1] The phenomenon was discussed at length by Kocher [9], whose authority was so considerable that iodide therapy of Graves' disease was virtually abandoned until it was reintroduced in 1923 by Plummer [12] However, by this time the work of Marine and Kimball [8, 10] had established the efficacy of iodide as a preventative of endemic goiter, and within the next few years large-scale prophylactic programs were instituted in many endemic areas of the world. The introduction of the prophylactic program in the United States was shortly followed by the appearance of a large number of reports describing an increased incidence of toxic goiter (McClure [11], Plummer [13], Kimball [7], Hartsock [4], Jackson [5, 6], and others). Whereas most of the reported cases followed the indiscriminate use of Lugol's solution or nostrums containing iodine, many were attributed solely to the use of iodized salt.

There are two possible consequences of the net positive balance of iodine exhibited by the three groups of patients described here:

1. An iodine-rich goiter could be produced;

2. The extrathyroidal pool of protein-bound iodine could be expanded: through increased hormone secretion the patient could become thyrotoxic.

The second possibility would be the current-day interpretation of the controversial phenomenon of jodbasedow. Quite possibly, as suggested by de Quervain [3], the likelihood of developing iodine-induced thyrotoxicosis depends upon the quantity of supplementary iodine. This hypothesis is consistent with the results reported here, where the net positive balance of iodine was lower when small supplements were given than when the patients received larger ones.

Single Supplements of Iodide

The foregoing observations were concerned with the net retention of iodine and the rate of approach to a new equilibrium when daily supplements of iodine were given. We shall now consider the effects of single doses of iodide on the uptake of labeled iodide given simultaneously.

Observations on 21 of our subjects can be used in a study of the effects of carrier iodide on the uptake of labeled iodide. Control uptakes were obtained in all. The groups that received 150 μg, 500 μg, and 1500 μg of iodine daily have already been mentioned. In these groups the second uptake determinations were made after a week of daily administration of iodide. Since in most patients seven days of supplemental iodide (the seventh day's supplement being given as carrier iodide for the second tracer dose) did not significantly change the uptakes from the control values, it seems hardly possible that a single iodide carrier of the same amount would have changed the uptake. Nine other patients with high control uptakes were selected and given second tracer doses with added carrier iodide. Three received 7 mg, three received 32 mg, and three received 150 mg of iodide.

The results are shown in Fig. 15. In accordance with the

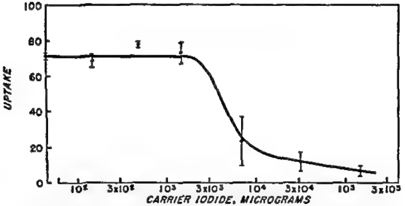

FIG 15. The effect of carrier iodide on the uptake of labeled iodide. The labeled iodide was given simultaneously with the carrier iodide. The uptake was either the 24- or 48-hour uptake, depending on which was higher Uptake is shown on the ordinate; on the abscissa is shown the quantity of carrier iodide in micrograms The vertical bars are the standard errors of the mean values

convention that has been adopted, the value for uptake is either the 24- or the 48-hour measurement, depending on which is higher. Had 48-hour uptake values alone been used, the three points at the right of the chart would have been lower by 2 to 6 per cent of the administered dose. It can be seen that carrier quantities of iodide up to 1.5 mg had very little effect on uptakes of these patients, but when larger quantities were used, the thyroid accumulated a small proportion of the dose.

Discussion. The influence of graded doses of iodide on the trapping of labeled iodine by the rat thyroid has been studied by Vanderlaan and Vanderlaan [16]. Their rats received propylthiouracil, a drug which prevents organic binding but does not prevent trapping of iodide. It was found that the ratio of labeled iodide in the gland to that in the serum was maintained at approximately 250 over a wide range of quantities of carrier iodide, but as the amount of carrier was increased further the ratio fell toward one. It appeared,

therefore, that the capacity of the gland to trap iodide was limited.

The effects of graded quantities of carrier iodide on thyroid function in thyrotoxic man have been studied by Childs *et al.* [2]. They found that there was no change in the proportion of iodide which was accumulated by the gland when the quantity of carrier iodide varied from a negligible amount to 100 μg. The thyroidal-accumulation curves of the tracers rose uniformly to reach their maxima in 8 to 24 hours. However, when 10 mg or more of iodide were given, the curve of iodine accumulation rose rapidly to a peak within 2 or 3 hours and thereafter decreased rapidly in a fashion to suggest that iodide was trapped, but not bound, and was returning to the blood from the iodide space of the gland as renal clearance lowered the iodide concentration of the blood. Doses of iodide between 0.75 and 2 mg gave accumulation curves that were intermediate between the two types. The authors' interpretation of these results was that the relative rate of synthesis of hormone, but not iodide trapping, may be suppressed when more than 100 μg of iodide is given at any one time, but that there was no evidence of a decrease in the absolute rate of hormone synthesis. Our findings of an unusually large fall in the quantity of accumulated iodine during the second 24 hours after large carrier doses of iodide are in accord with those of Childs *et al.*

Hormone synthesis may be suppressed by high concentrations of iodide in the blood. Wolff *et al.* [17] were able to demonstrate a virtually complete suppression of hormone synthesis in the rat when sufficient iodide was added to the diet to maintain a blood level above 35 μg per cent. The effect was transient, and could not be maintained longer than about two days. Stanley [15] has presented suggestive evidence that the same is true in normal and in thyrotoxic man, and that the blood concentration necessary to suppress hormone synthesis is less for the patient with Graves'

disease than for the normal. The implications of these findings for the theory of the effects of iodide in Graves' disease are not yet apparent, but it seems unlikely that this temporary inhibition of hormone synthesis can account for the sustained effect of large doses of iodide.

The simplest interpretation of our data is that the gland is limited in the quantity of iodine that it can utilize. In these patients it appeared that the absolute quantity of iodine which the gland was accumulating from a single dose was approaching a maximum as the quantity of carrier increased. The magnitude of this maximum cannot be estimated because of the relatively large error in measuring the uptake of labeled iodine accurately when the uptake is near zero, and because of the fact, already mentioned, that a part of the iodide accumulated from a large dose is rapidly lost from the gland and is probably never formed into hormone. However, our data lend no support to the alternative hypothesis that at high blood levels of iodide there is a specific impairment of the trapping of iodide or the binding of trapped iodide or both. Although the proportion of the labeled iodide accumulated by the thyroid decreased as the quantity of carrier increased, the *absolute amount* of iodide accumulated continued to increase.

Summary

1. Thirteen patients were divided into three groups. One hundred fifty micrograms of iodide were given daily to those of the first group, 500 to 600 to the second, and 1500 to the third. The uptake of labeled iodide and excretion of iodide were measured frequently.

2. There was a slow return toward a new balance between uptake and excretion of iodide over the ensuing weeks.

3. The rate at which equilibrium was approached was not governed by the size of the daily supplement. The net daily retention of iodide varied directly with the daily intake of

iodide, and the estimated total net positive balance of iodide at the new equilibrium was larger with larger supplements.

4. One of the patients who received 1500 μg of iodide daily developed frank thyrotoxicosis.

5. When iodide was added as carrier to tracer doses of labeled iodide, the proportion of the carrier that was accumulated by the thyroid was independent of quantity below 1.5 mg, but when larger quantities were given, progressively smaller fractions of the dose were accumulated.

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6

THE EFFECTS OF DESICCATED THYROID

Involutionary changes appear in the thyroid gland following the administration of desiccated thyroid. There is flattening of the acinar epithelium, relative increase in the quantity of colloid in the follicle, and diminution in the size of the gland. In addition, there is inhibition of thyroidal accumulation of labeled iodide. The classical interpretation of these phenomena is that the pituitary responds to a rising concentration of thyroid hormone in the blood by a decreased production of thyrotropic hormone. The reciprocal "feedback" control between the thyroid gland and the thyrotropin-producing cells of the pituitary is responsible for the day-to-day stability of the concentration of the thyroid hormone in the blood. In addition, a direct inhibitory effect by thyroxin on the thyroid has been described by Cortell and Rawson [1], but this is thought to be of relatively minor importance.

The enlarged thyroids exhibited by the iodine-deficient Mendoza patients presumably resulted from an attempt at compensation for the reduced dietary iodine supply. The sequence of events might be described as follows: The thyroid gland, supplied with an inadequate quantity of iodide from the blood, is unable to maintain a proper concentration of thyroid hormone in the blood. The thyrotropin-producing cells of the anterior pituitary, in response to a falling blood

content of thyroid hormone, produce more thyrotropin. This in turn causes growth and increased vascularity of the thyroid and acceleration of its metabolic processes, including an enhanced clearance of iodide from the blood. It might be expected that the administration of exogenous thyroid substance would reverse the train of events. It was of interest therefore to observe the effects of various doses of desiccated thyroid on the function of the thyroid glands of the Mendoza subjects.

Results

Six clinically euthyroid persons were chosen for the first series of observations. The average control uptake was 71.6 per cent, with a range from 68.8 to 74.5 per cent. The average control iodide excretion was 16.5 μg per 24 hours, with a range from 6.2 to 23.5. The uptakes and excretions of labeled iodide and iodide were measured at fortnightly intervals. During the first 2 weeks four of the patients received 32 mg of desiccated thyroid daily and the other two received 65 mg daily. For most of this period Armour's desiccated thyroid was employed. This preparation was not enteric-coated and was found to contain 0.2 per cent iodine. Through an unfortunate circumstance it was necessary for a few days to dispense an enteric-coated preparation which contained 0.3 per cent iodine. After the first two weeks each of the six patients received 0.1 gm of Armour's desiccated thyroid daily for the remaining two periods of approximately two weeks each.

Four of the six subjects failed to show a significant fall in uptake during the first two weeks (Fig. 16). The two patients who showed a drop in uptake were in the 32-mg group. The change in dosage after two weeks to 100 mg daily resulted in each case in a decrease in uptake. During the third period of approximately two weeks of continued treatment with 100 mg of desiccated thyroid daily, four subjects showed a

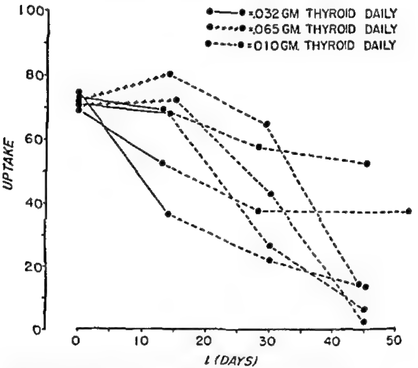
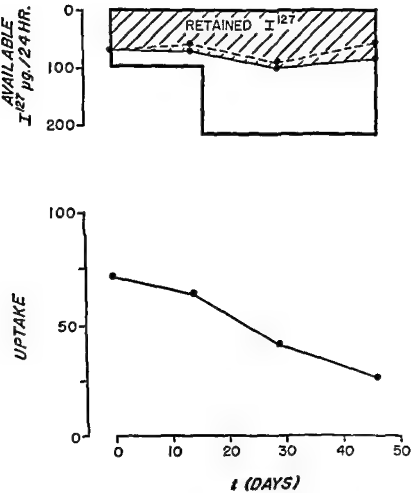


Fig. 16. The decline in uptake in six patients who received daily doses of desiccated thyroid as indicated.

further decline in uptake while two showed a very slight further fall.

The iodine balance of this group of six subjects is shown in Fig. 17. The average uptakes are shown on the lower curve. The average control uptake was 71.6 per cent, and after 46 days it was 26.4 per cent. The upper portion of Fig. 17 shows the average iodine intake during the study and the proportion of this which was retained by the patients. The average urinary excretion of iodide during the control period was 16.5 μg. The estimated iodide intake during the first two weeks of study is this control excretion value added to the total iodine in the ingested thyroid. The weighted average intake of iodide was therefore 102.3 μg.



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tained 200 μg of iodine. The lower curve shows the mean uptake. The upper diagram indicates the calculated retention of iodide. The solid line is calculated from the excretion of iodide. The dashed line is calculated from the uptake.

This neglects the fact that during a few days of these two weeks an enteric-coated preparation of thyroid containing 0.3 per cent instead of 0.2 per cent of iodine was used. During the second and third periods, when the daily dose was 100 mg, the average iodine intake was 216.5 μg. The balance curves were calculated as in Chapter 5. The solid line was obtained by subtracting the observed average iodide excretion from the theoretically available iodide. The dashed line was obtained by multiplying the iodine intake by the uptake. The solid balance line therefore depends upon iodide assay of the urine, while the dashed line depends upon uptake data.

The methods of calculation that have been employed require certain qualifications. The assumption was made that all the iodine in the desiccated thyroid entered the iodide pool of the body and was disposed of as iodide. However, an appreciable fraction of the iodine of desiccated thyroid may be excreted in the feces. If so, the solid balance lines of Fig. 17 should be corrected upward, depending upon the quantity of the total ingested iodine which was lost through the feces.

In addition, as pointed out in Chapter 5, the balance curve based on the uptake of labeled iodine must be corrected for urinary loss of iodide derived from the breakdown of endogenous hormone, for not only is the thyroid rejecting part of the dietary iodine $[In(1 - U)]$,* but it is also rejecting part of the iodide made available from the metabolism of thyroxine $[H(1 - U)]$.* The magnitude of this loss undoubtedly fell as hormone secretion fell as a result of pituitary inhibition by the exogenous hormone. All these corrections have the effect of moving the dashed line upward closer to the base line, but it is impossible to give them quantitative expression.

* *In*, iodine in the daily diet; *U*, fractional uptake; *H*, hormonal iodine secreted daily.

The average net positive balance of iodide for the 46 days of observation was calculated to be 3.93 mg. This figure is probably too high. The retained iodine may have been distributed in the thyroid, the blood, and other tissues, but since there was no detectable change in protein-bound iodine, most of the net gain must have been by the thyroid gland itself. The mean control protein-bound iodine was 6.1 μg per cent, and at the end of the experiment it was 6.6. (The final value was not obtained in one patient.)

Thyroid was more efficient in reducing the uptake of labeled iodide than was iodide. After 47 days of 150 μg of supplemental iodide, the uptake was reduced below 50 per cent in only two out of seven patients. After five to six weeks of 500 to 600 μg of supplemental iodide, the uptake was reduced below 50 per cent in only one of the three patients, and this patient began the study with an uptake of only 54.2 per cent. After 33 days of 1500 μg of supplemental iodide, the uptake had been reduced to less than 50 per cent in none of three patients. Yet after two weeks of doses of desiccated thyroid of less than 100 mg daily and two additional weeks of 100 mg daily, only two out of six patients had uptakes above 50 per cent. After two additional weeks four patients had uptakes of less than 20 per cent, and only one remained above 50 per cent. These various data have been averaged and are shown in Fig. 18. The quantity of iodide theoretically available from the administered thyroid could not account for the differences in the curves. The iodide content of the 100 mg dose of desiccated thyroid was 200 μg, or scarcely more than the lowest iodide supplement given to any of the three groups described in Chapter 5. Indeed, the average estimated intake of iodine in the thyroid supplement group was 8.36 mg after 46 days, whereas it was 7 46 mg after 46 days of 150 μg daily of supplemental iodide. The difference seems scarcely appreciable, yet the uptake of the thyroid group at this time was only 26 4 per

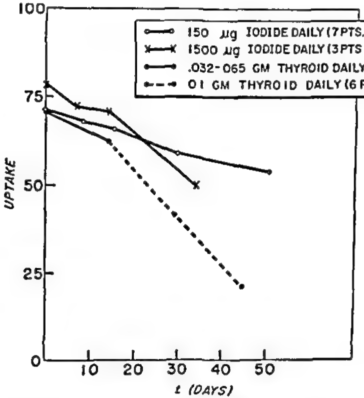

Fig. 18. The decrease in mean uptake in patients receiving the indicated doses of desiccated thyroid compared with patients receiving the indicated daily supplements of iodide. Note the faster decrease in the group receiving desiccated thyroid.

cent, whereas the interpolated uptake of the iodide group was 57 per cent after 46 days.

The effects of supplemental thyroid were observed in nine additional patients (Fig. 19). The control uptakes averaged 75.9 per cent, with a range from 69 per cent to 93 per cent. During the first two weeks each patient received 65 mg of desiccated thyroid daily. The dose was then increased to 100 mg daily for two to three more weeks, and

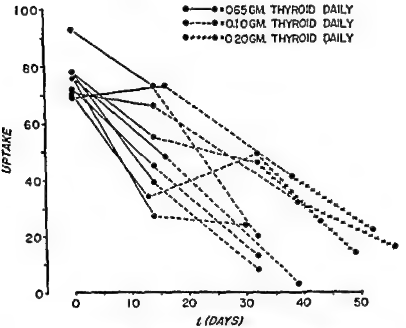

Fig. 19 The decrease in uptake in nine patients who received desiccated thyroid daily in the doses indicated

four patients were observed during an additional ten days to two weeks while receiving 200 mg daily. The uptake fell in seven out of nine patients during the initial period of 65 mg of thyroid daily. During the second period of 100 mg daily, eight out of nine patients, including the two who did not respond to 65 mg, showed a decrease in uptake, although in two of these the fall was slight. In four patients when the dosage was increased to 200 mg daily the uptakes declined still farther. All nine patients had uptakes of less than 50 per cent after 39 days of desiccated thyroid, and five of the nine had uptakes of less than 25 per cent by this time. The uptakes of all were reduced below 25 per cent by 0.2 gm or less of thyroid substance.

Discussion

A prominent feature of the results obtained from these two groups of patients was the variability of the response. This was also reported by Greer [2] and by Johnston *et al.* [3] in their studies on normal subjects. The observed variations could be due to differences in the sensitivity of the pituitary to the circulating thyroid hormone, to differences in the response of the iodine-deficient glands to changes in the quantity of thyrotropin in the blood, to differences in the efficiency with which the ingested thyroid is absorbed and utilized, or perhaps to other factors. Our patients seemed to respond more slowly than those of Greer. This suggests that part of the variability might be attributable to varying hormonal content or degree of hyperplasia of the glands.

The full effect of a given dosage of desiccated thyroid was not achieved in all subjects within two weeks. In four out of six patients of the first group, there was a significant further fall in uptake during the second two-week period of a daily dosage of 100 mg These results are to be compared with those of Greer [2], who found that 3 grains of thyroid daily produced a very nearly complete suppression of thyroid function after only 8 days. One might expect the more sluggish gland of the normal individual to be more easily suppressed. However, the results are not strictly comparable because the dosage employed by Greer was almost twice the maximum used in our first group of subjects. It would be of great interest to have additional data from normal subjects to compare with those obtained from the iodide-deficient Mendoza patients.

It is difficult to draw any conclusions from the iodide balance study. It was evident that desiccated thyroid caused a rapid diminution in the proportion of the available iodide that was retained by the body. For reasons that have already been given it is impossible to state with precision the rate

at which the new equilibrium was actually being approached. However, even neglecting the corrections that should have been made, it is clear that this was proceeding at a more rapid rate than with any of the iodide schedules noted in Chapter 5.

The inhibition of iodide uptake by desiccated thyroid was, for the most part, not due to the iodide *per se* contained in the medication. The fall in uptake was much faster than when supplementary doses of potassium iodide were administered. It would appear that the effect of desiccated thyroid is more directly on the pituitary-thyroid axis, whereas that of iodide is indirect by virtue of permitting an increased rate of thyroid hormone synthesis, which in turn resulted in less activity of the pituitary. Because of better inhibition of thyroid function, there was a smaller net positive iodide balance from desiccated thyroid than from daily doses of potassium iodide containing similar amounts of iodine. Its precise magnitude cannot be given, but its upper limit can be estimated. Presumably, there was an increase in the total iodine content of the thyroid gland.

There were few noteworthy clinical effects of the administered thyroid. One patient, a male of 33 years, demonstrated a remarkable melting away of a large goiter after several weeks of therapy. Only one of the patients admitted to any symptoms suggestive of overdosage. She complained of nervousness and tension while receiving 100 mg of thyroid daily.

Summary

1. The administration of desiccated thyroid results in a rapid fall in uptake by the iodine-deficient human thyroid gland.

2. The fall may be incomplete after two weeks.

3. There is extremely wide variability of response to a given dose of desiccated thyroid.

4. The rate of decrease of uptake could not be accounted for solely by the iodide contained in the desiccated thyroid.

5. Iodide-balance studies appeared to show an approach to a new equilibrium in patients receiving desiccated thyroid.

6. There was no evidence of increased sensitivity of these patients to desiccated thyroid.

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7

ADDITIONAL OBSERVATIONS

The program of study of endemic goiter in Mendoza encompassed several series of observations which were unrelated and of limited scope. The results of these are presented in this chapter. They include measurements of the effectiveness of methimazole (1-methyl-2-mercaptoimidazole) in blocking synthesis of hormone, very limited observations on a number of cretins, certain measurements on three of the authors, and assay of the renal clearance of iodide in three patients with endemic goiter.

The Effectiveness of Methimazole in Blocking Uptake

Determinations of uptake were made on seven clinically euthyroid patients. Each was then begun on methimazole. Two received 5 mg, three received 15 mg, and two received 30 mg, all at 8-hour intervals. Two hours after the initial dose of methimazole, each patient was given a second tracer. The second uptake was measured at 24 hours, and in two cases at 48 hours. Appropriate corrections were applied for the residual labeled iodine from the first tracer. The results are shown in Table V.

It can be seen that methimazole is an excellent agent for blocking the uptake of iodide. In one of the two patients who were taking 5 mg daily, the block was poor, but she had failed to take her third dose of the drug. The labeled iodine in her thyroid was scarcely affected by the administration

TABLE V. EFFECT OF METHIMAZOLE ON UPTAKE OF LABELED IODINE.

Patient	Dose of methimazole (mg/8 hours)	Uptake before methimazole (per cent)	24-hour uptake during methimazole (per cent)
1	5	57.7	36.2
2	5	67.6	10.6
3	15	51.6	8.7
4	15	59.0	10.8
5	15	50.8	7.8
6	30	45.3	2.8
7	30	55.5	2.9

of 300 mg of iodide given after the 48-hour uptake reading. The patients on 15- and 30-mg schedules showed virtually complete inhibition of uptake.

Observations on Cretins

An opportunity was afforded on two occasions to visit an institution for the care of defective persons. The clinical diagnosis for most of the inmates was cretinism. It was the general impression that the prevalence of cretinism had much diminished within the past few decades.

In this institution there were approximately 50 persons who fitted the common textbook descriptions of cretinism. Most were of short stature, ranging between three and one-half and four feet, but a few were slightly taller. All were exceedingly simple and evidently very happy. None could speak more than a word or two and most of them not at all. About one-half had visible enlargements of their thyroid glands, but none had a huge goiter. From skin temperature and texture, and from the pulse, one could not make a diagnosis of hypothyroidism.

It was not possible to pursue any detailed clinical observations on these patients. The only laboratory study that

could be made was the determination of the serum protein-bound iodine on thirteen of the cretins. The results are shown in Table VI.

TABLE VI. SERUM PROTEIN-BOUND IODINE IN THIRTEEN SUPPOSEDLY CRETINOUS SUBJECTS

Patient	Sex	P. B. I. (μg per cent)
E. R.	F	5.3
R. R.	F	3.9
P. R.	F	4.2
M. R.	F	14.4
A. G.	F	4.2
M. D.	F	10.5
H. T.	F	6.9
P. M.	F	5.4
C. R.	F	4.6
T. V.	M	3.8
A. P.	M	3.4
A. S.	M	4.4
F. A.	M	4.1

Most of these subjects had a normal concentration of protein-bound iodine in the serum, but two had abnormally high values. Careful questioning of the staff of the institution failed to disclose dietary or drug factors that might have accounted for the high determinations. Omitting the two high values, the mean protein-bound iodine concentration was 4.6 μg per cent.

The findings are similar to those of Vogliazzo, Viale, Scorta, and Marchis [6], who studied 21 patients who met the usual clinical criteria for a diagnosis of cretinism. Their patients had protein-bound iodine concentrations that varied between 3.4 and 7.3 μg per cent, and uptakes of labeled iodine that were in the low normal range.

It is obvious that these patients had managed to achieve virtually normal thyroid function as judged from the clinical evidences and the protein-bound iodine determinations. Perhaps during fetal life there had been a severe deprivation

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1	5	57.7	36 2
2	5	67.6	10 6
3	15	51 6	8 7
4	15	59 0	10 8
5	15	50.8	7.8
6	30	45 3	2 8
7	30	55 5	2 9

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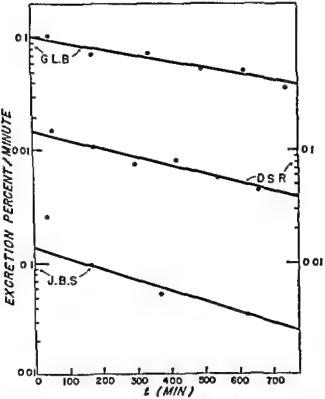

Fig 20 The excretion of labeled iodide by three of the authors in an area of iodine abundance The abscissa is time in minutes. The ordinate is excretion in per cent of administered dose of labeled iodine per minute.

The agreement between the observed and calculated uptakes is perhaps as good as could be expected in view of the fact that the tracers were given orally. However, the results were not sufficiently encouraging to warrant using this technique in Mendoza.

There were no significant changes in uptake after seven weeks of residence in Mendoza, despite a significant decrease in iodide excretion (Table VII). The slow approach to new equilibrium states during administration of supplements of

of iodine which prevented synthesis of an adequate quantity of hormone by either mother or fetus or both during a critical stage of gestation.

Incidental Observations upon Three of the Authors

In anticipation of a period of residence in Mendoza, three of the authors, G.L.B., D.S.R., and J.B.S., made observations upon themselves of uptake and excretion of labeled iodine and excretion of iodide while in Boston, with the expectation of repeating the observations shortly before leaving Mendoza. It was hoped that the change in dietary iodide might be of sufficient magnitude to result in changes in thyroid function.

From the half time, $T\frac{1}{2}$, of the urinary-excretion curve of labeled iodide plotted as per cent of dose per minute, the total disposal rate of labeled iodine $(k_1 + k_2)$ can be calculated:

$$(k_1 + k_2) = \frac{0.693}{T\frac{1}{2}}. \tag{7.1}$$

It will be recalled that 0.693 is the natural logarithm of 2. In this equation k_1 is the rate constant of thyroid disposal of labeled iodide and k_2 that of renal disposal (cf. Chapter 8). The urinary-excretion curve extrapolated to zero time intercepts the ordinate at the renal disposal rate, k_2, in per cent of dose per minute. By difference one can find k_1, the thyroid disposal rate, and from the two parameters calculate the uptake, U, since *

$$U = \frac{k_1}{(k_1 + k_2)}.$$

These studies were conducted on the three subjects in Boston, and, in addition, routine uptakes and 48-hour excretions were measured. The urinary excretion curves are shown in Fig. 20, and the parameters are given in Table VII.

* See Chapter 8 for a derivation of this equation, Eq. (8 14).

The Renal Clearance of Iodide

The competition that exists between the thyroid gland and the kidneys for the available supply of iodide was described in Chapter 3 [1]. Because of this competition, compensation for a decreased intake of iodide could hypothetically be achieved either by an increase in the clearance of iodide by the thyroid or by a decrease in the clearance of iodide by the kidneys, or by both. The hypertrophy and hyperplasia of the thyroid gland of patients with endemic goiter are accompanied by a corresponding increase in blood supply and very possibly in the efficiency with which the gland extracts iodide from the blood. These changes produce an increase in the thyroidal clearance of iodide.

In man there is no renal threshold for iodide excretion. In regions where the supply of iodide is abundant, the mean concentration of iodide in the plasma is only about 0.3 μg per 100 ml. Despite this minute concentration, the kidneys clear iodide from the plasma as rapidly as when the concentration is deliberately raised by the administration of large doses of iodide [2]. While it is true that the renal clearance of iodide tends to be subnormal in patients with myxedema, the patients studied in Mendoza presented no significant evidence of hypothyroidism. Nevertheless, it seemed worth while to test the possibility that some kind of renal adaptive mechanism for conservation of iodide might be encountered when the plasma iodide falls to the vanishingly small concentrations characteristic of a region of iodine deficiency.

The renal clearance of iodide was measured in three patients who had thyroid glands that were to be removed surgically. Seven hundred microcuries of radioactive iodide were administered by mouth and serial measurements of the labeled iodine in plasma and urine were made at intervals thereafter. From these measurements the renal clearance of

TABLE VII. METABOLISM OF IODINE IN THREE EUTHYROID SUBJECTS STUDIED IN BOSTON AND IN MENDOZA.*

Subject	*Values calculated from curves of Fig 20 (Boston)* $k_1 + k_2$ (%/hour)	k_2 (%/hour)	k_1 (%/hour)	Calculated uptake (per cent)	Observed uptake (per cent) Boston	Mendoza
G L.B.	7 44	6 12	1 32	17.8	31 5	35 7
D S.R.	10.28	9 0	1.28	12 5	15 2	12 9
J B S	13 44	8 1	5 34	39 2	28 0	27.1

	Observed excretion of labeled iodide in 48 hours (per cent)		48-hour recovery of labeled iodide (per cent)		Mean excretion of iodide † ± standard error of mean (μg/day)	
	Boston	Mendoza	Boston	Mendoza	Boston	Mendoza
G L B.	52 3	62 7	83.8	88 0	144 ± 15 5	88 8 ± 7.2
D S R.	85 4	83 7	100 6	96 6	335 ‡	138 ± 6 7
J B S.	71 4	65 9	99 4	93 0	146 ± 18 2	86 2 ± 4 5

* k_1 is the thyroid disposal rate of iodide and k_2 the renal disposal rate. [illegible] obtained from Eq. (8.14)

in the Mendoza series.

‡ Subject on iodized salt This figure is the result of a single analysis of a pool of seven 24-hour urine specimens

iodide to the patients of Chapter 5 will be recalled. There is no *a priori* reason to suppose that the reverse condition, that is, a sudden deprivation of dietary iodine, would not be met by a very slow rise in uptake. The excretions of iodide by these three subjects in Mendoza could have been largely derived from hormone degradation rather than from the daily diet. This would correspond to a negative iodine balance in contrast to the patients of Chapter 5. The assumption that intake and excretion are nearly equal is valid only at equilibrium. These three subjects were not in equilibrium.

iodide was calculated in the usual fashion. The results are shown in Table VIII. The clearance rates are within the normal range for subjects living in regions of relative iodine abundance [3, 4, 5]. It appears, therefore, that renal conservation of iodide does not play a part in the compensatory adjustments to iodine deficiency.

The results of the observations on these three subjects are shown graphically in Fig. 21–23. The labeled iodine content of the thyroid, serum, and urine were measured frequently during the first three hours and daily thereafter for four days. The charts illustrate the rapid accumulation and high uptake of the labeled iodine, and the parallel decline in blood concentrations of labeled iodine and its appearance in the urine.

After the second day the blood concentration of labeled iodine rose in all three patients. This presumably occurred as labeled hormone entered the blood.

Summary

1. The antithyroid drug methimazole is effective in preventing uptake of labeled iodine by the thyroid in subjects with endemic goiter.

2. The mean serum concentration of protein-bound iodine of thirteen cretins was within normal limits, but there was a wide range of values. Cretinism in this group presumably resulted from severe iodine deprivation during a critical stage of fetal life.

3. Three normal subjects showed a fall in mean iodine excretion when they went from Boston to Mendoza, but there was no significant change in uptake during the limited period of residence in the iodine-deficient area.

4. The renal clearance of iodide was found to be normal in three iodine-deficient human subjects with goiter.

TABLE VIII. RENAL CLEARANCE OF IODIDE IN THREE PATIENTS WITH ENDEMIC GOITER.

Patient	Time after tracer (min)	Plasma labeled iodine (per cent of dose per liter)		Urinary labeled iodine (per cent of dose per min)	Renal clearance (ml of plasma per min)
		Observed	Calculated mean*		
M M.	15	0 87			
	45	1 94			
	30–60		(2 00)	0 0533	(27)
	75	1 66			
	60–90		1.56	.0436	28
	105	1.14			
	90–120		1.23	.0294	24
	135	0 97			
	120–150		0 96	.0217	23
					Mean 25
J. S	16	2 23			
	45	1 98			
	31–62		1 94	0 0618	32
	76	1.57			
	62–92		1 68	.0486	29
	109	1 50			
	92–122		1.45	0396	27
	136	1.29			
	122–151		1.27	.0341	27
					Mean 29
A. M.	20	1.53			
	50	1.98			
	35–65		(1.98)	0.105	(53)
	80	1.72			
	65–95		1.74	.0735	42
	110	1.53			
	95–125		1.54	.0778	51
	140	1 34			
	125–155		1 34	.0532	40
					Mean 44

* [illegible] concentration of labeled iodide in the plasma for each urine [illegible] portion of the plasma curve. The plasma concentrations at the beginning (P_1) and end (P_2) of the urine collection period were calculated from this line. The logarithmic mean plasma concentration was then calculated from the equation:

$$\text{Mean plasma concentration} = (P_1 - P_2)/\ln(P_1/P_2).$$

The urinary excretion rate was then divided by the mean plasma concentration per milliliter to obtain the renal plasma clearance in milliliters per minute. The values in parentheses were obtained by extrapolating the *straight line* beyond the initial point upon which it was based and have therefore been omitted from the averages.

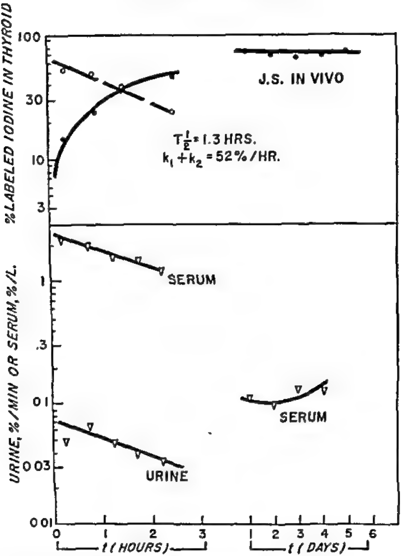

Fig. 22 *In vivo*, serum, and excretion data for patient J. S. For details of plotting, see legend for Fig. 21.

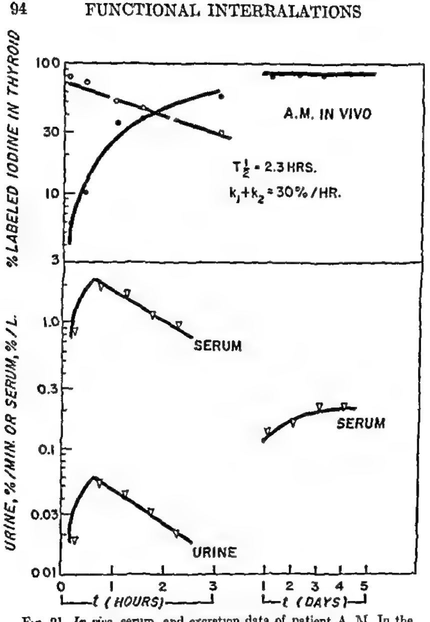

Fig. 21. *In vivo*, serum, and excretion data of patient A. M. In the

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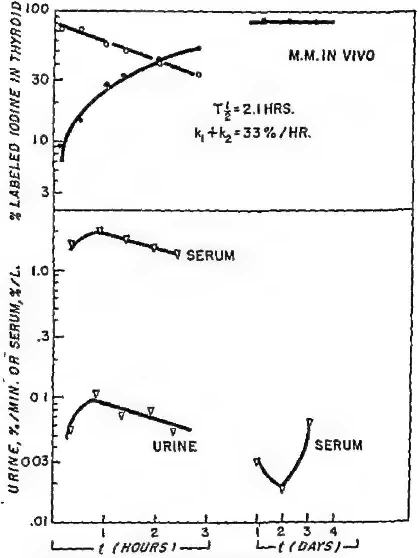

Fig. 23. *In vivo*, serum, and excretion data for patient M. M. For details of plotting, see legend for Fig 21.

PART III

DYNAMICS OF IODINE METABOLISM

8

THEORETICAL ASPECTS OF IODINE METABOLISM

The metabolic studies described in Part II were based primarily upon measurements of the daily excretion of iodide, E, and the uptake, U. Although the uptake is most conveniently calculated from the distribution of a tracer dose of labeled iodide, it could theoretically be obtained by administering a small amount of iodide to a subject on a constant iodide intake and determining chemically the proportion of the dose excreted in the urine. However, for the elucidation of certain dynamic aspects of iodine metabolism, labeled iodine is indispensable. For example, only with labeled iodine can one determine what fraction of the organic iodine stored in the thyroid gland is transferred to the extrathyroidal tissues per unit time. Also, from this proportional rate of transfer (defined below as the rate constant, k_4) and from the absolute rate of transfer, H, it is possible to calculate the quantity of organic iodine present in the intact thyroid gland. This chapter will be devoted to a theoretical discussion of the dynamic behavior of iodine in the three-compartment model described in Chapter 3. The concepts thus developed will be used for the interpretation of the experimental results presented in the next three chapters.

Since the analysis that follows is based upon the three-compartment model of iodine metabolism, it should be

For illustrating the dynamic properties of the three-compartment system of iodine metabolism, Fig. 24 is a convenient alternative to Fig. 6 (Chapter 3). The compartments have the same significance as before, but no attempt has been made to illustrate their relative sizes. Interchanges

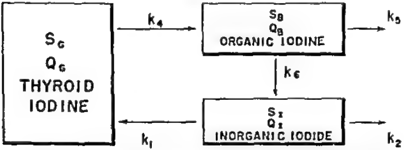

Fig. 24. A diagram to illustrate the dynamic properties of the three iodine-containing compartments of the body after the administration of labeled iodine. The constants, k, are the rate constants of transfer between compartments, S is specific activity, and Q is iodine content. Subscripts G, B, and I refer to thyroid, extrathyroidal organic, and inorganic iodine compartments, respectively

between compartments are represented by rate constants. For example, the proportion of the organic iodine in the thyroid that enters the compartment of organic iodine in the extrathyroidal tissues per day is the rate constant k_4. If the total quantity of organic iodine in the thyroid be designated as Q_G, the rate of secretion of hormonal iodine is k_4Q_G. Similarly, the rate of secretion of labeled iodine is $k_4Q_G^*$.

With this notation, the fate of labeled iodine in the model illustrated by Fig. 24 may be exactly represented by the following differential equations:

$$\frac{dQ_I^*}{dt} = -(k_1 + k_2)Q_I^* + k_6Q_B^*, \tag{8.1}$$

$$\frac{dQ_G^*}{dt} = -k_4Q_G^* + k_1Q_I^*, \tag{8.2}$$

$$\frac{dQ_B^*}{dt} = -(k_5 + k_6)Q_B^* + k_4Q_G^*. \tag{8.3}$$

obvious that the relations derived will fit experimental facts only when the simplifying assumptions explicitly stated in Chapter 3 are reasonably valid. In general, the agreement between theory and observation is sufficiently good to justify the use of calculations based upon the simple model. However, *when the quantity of hormone stored in the thyroid gland is small*, the assumption that all of the organic iodine in the thyroid behaves as a single homogeneous compartment seems to be inconsistent with the observed behavior of labeled iodine, and it becomes necessary to postulate an additional compartment. (See Chapter 9.) This clearly illustrates the limitations inherent in the term "compartment." When the iodine that was originally assigned to a single compartment no longer follows the predicted pattern of behavior, the compartment must be subdivided. From the physiological standpoint, subdivision presents no conceptual difficulties since each of the three compartments has already been defined as an abstract composite of many more or less distinct real units whose *average* behavior determines the behavior of the compartment. But as more and more compartments are added, the equations required soon become forbiddingly complex and cease to be useful.

It is essential at this point to introduce the concept of *specific activity*. Specific activity is here defined as the ratio of the quantity of labeled iodine to the total quantity of iodine within a compartment. The statement is often made that, as time passes, the specific activities in multicompartment systems approach equality. Actually, when the continued intake and excretion of unlabeled material are important factors, the specific activities in any two compartments are equal only for one particular instant of time. However, the specific activities of any two compartments do approach a constant ratio (secular equilibrium), and when this ratio is close to unity, the assumption of equal specific activities is a legitimate and useful approximation.

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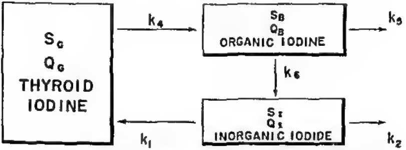

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$$\frac{dQ_G^*}{dt} = -k_4Q_G^* + k_1Q_I^*, \tag{8.2}$$

$$\frac{dQ_B^*}{dt} = -(k_5 + k_6)Q_B^* + k_4Q_G^*. \tag{8.3}$$

For definitions of symbols used here and subsequently, the reader is referred to Table IX.

It is worth noting that while these equations might equally well be written in terms of total iodine simply by omitting the asterisks and including an expression for iodide intake, the differentials would all be equal to zero when the system was in a steady state of iodine equilibrium. The equations are useful, therefore, only when they describe the behavior of a particular group of iodine atoms introduced as labeled iodide into the iodide compartment at time zero.

As defined above, the specific activity, S, in any compartment is Q^*/Q. Hence:

$$Q^* = QS, \tag{8.4}$$

and Eqs. (8.1), (8.2), and (8.3) may accordingly be transcribed in terms of specific activities:

$$Q_I \frac{dS_I}{dt} = -(k_1 + k_2)Q_I S_I + k_6 Q_B S_B, \tag{8.5}$$

$$Q_G \frac{dS_G}{dt} = -k_4 Q_G S_G + k_1 Q_I S_I, \tag{8.6}$$

$$Q_B \frac{dS_B}{dt} = -(k_5 + k_6)Q_B S_B + k_4 Q_G S_G. \tag{8.7}$$

In general, this set of simultaneous equations cannot be solved in a convenient closed form. However, under carefully specified circumstances useful approximations may be made based on certain limiting assumptions.

The Uptake of Labeled Iodine

The rate constant for accumulation of iodide by the thyroid, k_1, and the rate constant for the renal excretion of iodide, k_2, are almost invariably much larger than the rate constant for secretion of organic iodine, k_4. Therefore, immediately after the administration of unit quantity of labeled iodide, the rate constant for secretion may be as-

TABLE IX. SYMBOLS, UNITS AND DEFINITIONS.

The following symbols are used for expressing symbolically the parameters of thyroid function and for the derivations of their interrelations. The rate constants are defined as the fraction of the iodine of one compartment entering another in unit time. These fractions are at times multiplied by 100 and expressed as percentages, but in equations always appear as fractions Each of these constants may also be characterized by a half-time, which is the time required for the amount of labeled iodine in the compartment to decrease by one-half, assuming only one route of loss The half-time may be found by dividing 0 693 (the natural logarithm of 2) by the rate constant

Symbol	Unit	Definition
I	none	Iodide compartment
G	none	Thyroid organic iodine compartment
B	none	Extrathyroid organic iodine compartment
Q_I, Q_G, Q_B	microgram	Total quantity of iodine in I, G, B
Q_I^*, Q_G^*, Q_B^*	fraction	Fraction of dose of labeled iodine in I, G, B
S_I, S_G, S_B	fraction/microgram	Specific activity in I, G, B
In	microgram/day	Daily intake of iodide
H	microgram/day	Rate of secretion of hormonal iodine
E	microgram/day	Rate of excretion of iodide by kidney
F	microgram/day	Rate of excretion of organic iodine †
H^*	fraction/day	Fraction of dose of labeled iodine secreted as hormone per day
E^*	fraction/day	Fraction of dose of labeled iodine excreted by kidney per day
k_1	fraction/unit time	Rate constant of thyroid accumulation of iodide from iodide space
k_3	fraction/unit time	Rate constant of renal excretion of iodide from iodide space
k_4	fraction/unit time	Rate constant of secretion of organic iodine from thyroid
k_4'	fraction/unit time	Rate constant of net loss of labeled iodine from thyroid when the ratio of the specific activities in G and B has become constant
k_5	fraction/unit time	Rate constant of excretion of organic iodine from B
k_6	fraction/unit time	Rate constant of breakdown of hormone in B to inorganic iodide
U	fraction	Uptake fraction of labeled iodide in I entering thyroid
t	hours *or* days	Time

† Chiefly fecal, and therefore sometimes referred to as "fecal excretion of iodine" in the text.

sumed to be zero. Consequently there will be no labeled iodine in the extrathyroidal tissues ($S_B = 0$), and Eq. (8.5) becomes

$$\frac{dS_I}{dt} = -(k_1 + k_2)S_I. \tag{8.8}$$

Solving for S_I we obtain

$$S_I = S_{I_0}e^{-(k_1+k_2)t}, \tag{8.9}$$

where S_{I_0} designates the specific activity of the iodide compartment at zero time. But since unit quantity of labeled iodine was administered at time zero, by definition

$$S_{I_0} = \frac{Q^*_{I_0}}{Q_I} = \frac{1}{Q_I}, \tag{8.10}$$

and Eq. (8.9) becomes

$$S_I = \frac{1}{Q_I}e^{-(k_1+k_2)t}. \tag{8.11}$$

At any instant of time, the rate at which labeled iodine is being taken up by the thyroid will be given by Eq. (8.2). Since k_4 is assumed to be zero, Eq. (8.2) may now be written:

$$\frac{dQ^*_G}{dt} = k_1Q^*_I = k_1Q_IS_I. \tag{8.12}$$

Substituting in this equation the value for S_I from Eq. (8.11) gives

$$\frac{dQ^*_G}{dt} = k_1e^{-(k_1+k_2)t}. \tag{8.13}$$

Now the uptake U is defined as the total quantity of labeled iodine that would be accumulated by the thyroid in infinite time *on the present assumption that there is no loss of labeled iodine from the gland.* Hence, the total uptake may be found by integrating Eq. (8.13) (the instantaneous rate of uptake) over time from zero to infinity:

$$U = \int_0^\infty k_1e^{-(k_1+k_2)t}dt = \frac{k_1}{k_1 + k_2}. \tag{8.14}$$

This equation seems self-evident without derivation. The uptake is thus seen to be the rate constant for iodide accumulation in the thyroid divided by the sum of this rate constant and the rate constant for renal excretion of iodide. Since these rate constants are proportional to the corresponding plasma clearances, the uptake could equally well be defined as the ratio of the thyroid clearance to the total clearance of iodide from the plasma. As such, it represents a fundamental parameter of thyroid activity.

The uptake defined by Eq. (8.14) is more properly termed the *theoretical uptake*. In actual practice the accumulation of labeled iodine by the thyroid will never reach the theoretical uptake because the rate of secretion of labeled hormone is not, in fact, zero, and some labeled iodine will be lost from the gland before accumulation is complete. However, when the turnover of hormone in the thyroid is slow, the observed uptake is very close to the theoretical uptake. For example, in a normal subject with some 8000 μg of organic iodine in the thyroid, the half-time of labeled iodine in the gland is of the order of 100 days, and the observed uptake is practically indistinguishable from the theoretical uptake But when the store of hormone is greatly depleted, as in certain patients with severe and prolonged iodine deficiency, turnover may be so rapid that the observed uptake is no longer a satisfactory approximation of the theoretical uptake.

Approximations for Specific Activities Following Initial Accumulation of Labeled Iodide

Following the accumulation of labeled iodide by the thyroid, labeled hormone is secreted at the rate k_4 per cent per day. As the labeled hormone begins to be metabolized in the tissues, some of the iodine released will reënter the thyroid and decrease the *net* rate of loss of labeled iodine from the gland. Thus, the final net rate of loss, k_4' per cent per day, which is approached with the passage of time, is always

less than k_4, the initial rate of loss, and if the amount of labeled iodine remaining in the gland is plotted logarithmically against time, the curve will be biphasic. The change in slope is large when the uptake is high, but even then may not be evident experimentally if the initial release rate, k_4, is small.

It is impossible to obtain convenient, closed solutions for the differential equations describing the specific activities of the three compartments for the period following the accumulation of labeled iodide [Eqs. (8.5), (8.6), and (8.7)]. However, in certain situations it is experimentally impossible to distinguish the biphasic nature of the thyroid retention curve, and under these conditions the assumption of a simple exponential thyroid decay curve is legitimate. An analysis of this simplified case is warranted by the insight it gives into the rather complicated dynamics of thyroid hormone metabolism.

Equations for the specific activities of the three compartments have been derived in Appendix B on the basis of the following assumptions: (1) that the thyroid specific activity has the initial value (U/Q_G) and *decays* at the single rate k_4', although the thyroid *secretes* hormone at the rate k_4; (2) that transfer of iodide from the iodide compartment to the thyroid does not occur ($k_1 = 0$), except in so far as such transfer is implied by using k_4' instead of k_4 as the rate constant for loss of labeled iodine from the thyroid; and (3) that there is no excretion of organic iodine ($k_5 = 0$). The specific activities are given by the following equations:

$$S_G = \frac{U}{Q_G} e^{-k_4't}, \tag{8.15}$$

$$S_B = \frac{k_4 U}{(k_6 - k_4')Q_B} e^{-k_4't}[1 - e^{-(k_6-k_4')t}], \tag{8.16}$$

$$S_I = US_B. \tag{8.17}$$

From Eq. (8.17) it is evident that the ratio of the specific activity in the iodide compartment, S_I, to that in the com-

partment of organic iodine in the extrathyroidal tissues, S_B, is simply the uptake, U. It is less than unity because labeled iodine derived from hormone breakdown is diluted with unlabeled dietary iodide, and it rapidly assumes the constant value U, because the turnover of iodine in the iodide compartment is rapid.

If k_4, the thyroid release constant, is small in comparison with k_6, the rate constant of hormonal degradation, the ratio of specific activity in the extrathyroidal tissues to that in the thyroid is:

$$\frac{S_B}{S_G} = \left(1 + \frac{k_4'}{k_6}\right)[1 - e^{-(k_6 - k_4')t}]. \tag{8.18}$$

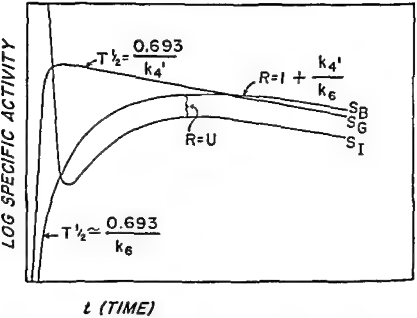
The term in brackets approaches unity with a half-time approximately $(0.693/k_6)$ if k_6 is large compared with k_4', and the ratio approaches the constant value $(1 + k'/k_6)$, which is somewhat greater than unity. This constant value is usually close enough to unity to justify the assumption that the specific activities are equal, but it must be kept in mind that this is true only when the time since administration of labeled iodine is considerably greater than $(0.693/k_6)$ so that the exponential term in Eq. (8.18) is negligible.

The relation between the net thyroid release rate, k_4', and the true release rate, k_4, is also derived in Appendix B and is approximately

$$k_4' = k_4\left[1 - \left(1 + \frac{k_4'}{k_6}\right)U\right]. \tag{8.19}$$

If the specific activities are assumed equal, it is seen to be equally valid to assume that the ratio of k_4' to k_4 has the simple form $(1 - U)$.

Figure 25 illustrates schematically some of the features described by Eq. (8.15)–(8.19) as well as the initial iodide accumulation. After the initial collection of labeled iodine is complete, the specific activity of the thyroid compart-



[illegible] specific activity, S_G, then falls slowly at a rate, k_4', which corresponds to a half-time of $0.693/k_4'$. The specific activity, S_B, of hormone in extrathyroidal tissues rises at a rate controlled initially by k_6, crosses S_G, and approaches a constant ratio to S_G approximated by $(1 + k_4'/k_6)$. After its initial drop, S_I maintains a constant ratio U to S_B.

ment, S_G, drops uniformly at the rate k_4'. Its biological half-time, $T\frac{1}{2}$, is therefore $0.693/k_4'$. The specific activity of the hormonal iodine in the extrathyroidal tissues, S_B, approaches that of the thyroid at a rate initially controlled by k_6, the rate constant for metabolism of hormone in the tissues. Ultimately it slightly exceeds the specific activity in the gland, and thereafter these two curves are separated by the constant ratio $1 + (k_4'/k_6)$. The specific activity of the iodide, S_I, falls rapidly at first as it is accumulated by the thyroid and excreted by the kidneys. Thereafter, it follows the shape of

the curve for the extrathyroidal tissues, but is separated from it by a constant ratio equal to the uptake, U.

Although these calculations reveal some of the general features of the dynamic behavior of iodine in the three-compartment model, several of the assumptions upon which they are based become less and less valid as the rapidity of iodine turnover in the thyroid gland increases. In lieu of a rigorous mathematical solution of Eqs. (8.5), (8.6), and (8.7), calculations have been performed by means of an analogue computer. Results of such calculations will be presented in Chapter 9. The theory of the analogue computer has been described in detail elsewhere [1] In essence it is a capacitative electric network so constructed that the flow of charge from capacitor to capacitor simulates the transfer of labeled iodine from compartment to compartment. The various capacitances are made proportional to the quantities of iodine present in the corresponding compartments, and the resistances between capacitors are chosen to correspond with the rates of transfer of electric charge. At zero time, unit charge is put into the capacitor representing the iodide compartment just as unit quantity of labeled iodide is put into the iodide compartment itself in the biological system. As the electric charge travels from capacitor to capacitor, the transient voltages produced are proportional to the specific activities of the corresponding compartments. The voltage curves of all capacitors are simultaneously visible on the screen of an oscilloscope. With this apparatus it is possible to see whether the behavior of labeled iodine actually observed in a given patient conforms to the pattern expected in the particular biological model simulated by the analogue computer.

Calculation of the Quantity of Organic Iodine in the Thyroid Gland

A calculation of thyroid iodine content, Q_o, may be made by assuming equal specific activities in the thyroid iodine

and extrathyroidal hormone compartments. Under these circumstances, the specific activity of the urinary iodine will equal that of the iodide compartment from which it is derived, and will be

$$\frac{E^*}{E} = S_I = US_B = US_G = \frac{UQ_G^*}{Q_G}, \tag{8.20}$$

and

$$Q_G = \frac{EU}{E^*/Q_G^*}. \tag{8.21}$$

Thus the quantity of iodine in the gland may be calculated from the uptake, the excretion of iodide, and the ratio of urinary excretion of labeled iodide to the labeled iodine remaining in the thyroid. In practice (cf. Chapters 9, 10, and 11), the urinary excretion of iodide, E, was averaged over the entire period of observation, and the ratio of labeled iodine in urine and gland, E^*/Q_G^*, was averaged over the period during which it seemed to be reasonably constant. Actually, in most cases, random day-to-day variations in the excretion of labeled iodine made it impossible to determine the shape of the curve obtained by plotting E^*/Q_G^* against time. Consequently, the average was taken over the whole period of observation excluding only the initial few days during which labeled iodine not derived from hormone breakdown was still being cleared from the iodide compartment.

The quantity Q_G may also be derived from the rate constant of secretion of hormone, k_4. By definition,

$$Q_G = \frac{H}{k_4}. \tag{8.22}$$

If excretion of organic iodine is neglected, the approximate form of Eq. (8.19) may be used to replace k_4 by k_4'; thus,

$$Q_G = \frac{H(1 - U)}{k_4'}. \tag{8.23}$$

Furthermore, $H(1-U)$ can be replaced by UE from Eq. (4.4), giving

$$Q_G = \frac{UE}{k_4'}. \tag{8.24}$$

Comparison of Eqs. (8.21) and (8.24) reveals that

$$k_4' = \frac{E^*}{Q_G^*}, \tag{8.25}$$

which states that the net rate of release of labeled iodine from the thyroid is equal to the fraction of the labeled iodine of the thyroid that is excreted per day.

Although Eq. (8.24) is equally valid for the computation of Q_G, in general the quantity E^*/Q_G^* can be measured more accurately than the net release rate, k_4', and therefore is preferred.

The quantity Q_G can also be calculated by a method involving measurements of the excretion of iodide and of labeled iodide and of the retention of labeled iodide after administration of methimazole. This method, which is independent of measurement of uptake, will be described in Chapter 10.

Calculation of the Daily Secretion Rate of Hormonal Iodine

We have seen in Chapter 4 that H, the rate of secretion of hormonal iodine, may be calculated for individual subjects by means of Eq. (4.4), or for a group of subjects by a graphical method employing Eq. (4.5). Theoretically, it should be possible to calculate the rate of secretion of hormonal iodine from the thyroid gland by observing the increase in excretion of urinary iodide when the synthesis of hormone is blocked by the administration of a drug such as 1-methyl-2-mercaptoimidazol (methimazole), which inhibits synthesis of the organic iodine components of the gland. It is necessary to assume that the sole action of the drug is to

inhibit the uptake of iodide for the synthesis of hormone, an assumption not supported by the data of Chapter 10. If the uptake by the blocked gland is U_{bl}, and the urinary excretion during the block is E_{bl}, the urinary excretion will equal the proportion excreted multiplied by the amount entering the iodide compartment:

$$E_{bl} = (1 - U_{bl})(In + H - F). \tag{8.26}$$

The daily intake is In, the hormonal iodine secretion is H, and the fecal excretion of iodine is F. Combining Eqs. (4.2) and (8.26) and solving for H, we have

$$H = \frac{E_{bl}}{1 - U_{bl}} - E_0, \tag{8.27}$$

where E_0 is the mean daily urinary excretion before the block. If the block is complete, U_{bl} becomes equal to 0 and the equation reduces to

$$H = E_{bl} - E_0. \tag{8.28}$$

Again assuming that the only action of the blocking agent is to inhibit the uptake of iodide for the synthesis of hormone, the ratio of urinary iodide excretion after and before the administration of the drug may be calculated:

$$\frac{E_{bl}}{E_0} = \frac{1 - U_{bl}}{1 - U}, \tag{8.29}$$

which approaches $1/(1 - U)$ as U_{bl} approaches 0. This equation gives the relative increase in excretion rate of iodine that would be expected after administration of a drug which completely blocks synthesis. Similarly, it gives the relative increase in excretion rate of labeled iodine under the same circumstances or after very large doses of iodide, providing the thyroid and peripheral organic compartments have reached states of equal or nearly equal specific activity.

If the thyroid content, Q_G, is known, and F, the fecal excretion, is neglected, H may be calculated directly from

the observed rate of release k_4' by a rearrangement of Eq. (8.23):

$$H = \frac{k_4'}{(1 - U)} Q_G. \tag{8.30}$$

The rate constant k_4' may be directly determined from the slope of the thyroid retention curve, or it may be determined as indicated by Eq. (8.25) from the average value of the quantity E^*/Q_G^*; then

$$H = \frac{Q_G}{1 - U}\left(\frac{E^*}{Q_G^*}\right). \tag{8.31}$$

If the gland is suddenly blocked, and k_4 is assumed to equal $(k_4')_{bl}$, H may be calculated using the observed rate of release, $(k_4')_{bl}$, of the blocked gland:

$$H = (k_4')_{bl} Q_G. \tag{8.32}$$

Again, k_4' may be determined from the average value of $(E^*/Q_G^*)_{bl}$ measured over the period of block (bl). Then

$$H = Q_G\left(\frac{E^*}{Q_G^*}\right)_{bl}. \tag{8.33}$$

For this equation to be useful, Q_G must be calculated by some means other than Eq. (8.21); otherwise this equation simply reduces to Eq. (4.4). An equation for Q_G suitable for use with Eq. (8 33) will be derived in Chapter 10 [Eq. (10.3)]. This formulation has the disadvantage of involving the assumption that the rate at which iodine leaves the gland remains unchanged after the block. The data of Chapters 10 and 11 indicate that this is not true.

Most of the derivations which have been presented in this chapter are based upon the assumption that the system is in iodine equilibrium, that is, that the amount of iodine in each compartment remains constant. The administration of any drug that influences thyroid function will upset the equilib-

rium and formally negate all of the previous theory. Practically, however, the concepts developed here, with appropriate modifications, can often be used for the interpretation of nonequilibrium states. If, during the administration of a drug, the thyroid retention curve assumes a new simple exponential slope, and if the ratio of labeled iodide in the urine to that in the gland, E^*/Q_G^*, assumes a new value but then remains constant, it seems legitimate to assume that the model is unchanged except for the rate constants. This situation cannot be expected to last indefinitely, but usually the turnover time in the thyroid is long enough to allow observations to be made before the model itself is changed. Further discussion of nonequilibrium states will be found in Chapters 10 and 11, where the results of administering methimazole, thyrotropic hormone, and large doses of iodide are described.

Summary

1. Mathematical analysis based upon the three-compartment model of thyroid function leads to a variety of relations involving the parameters of glandular activity. It is shown, for example, that by a suitable choice of accessible data it is possible to calculate the daily secretion rate of hormonal iodine and the quantity of iodine in the thyroid gland.

2. The theoretical uptake, defined by the relation between the rate constants of disposal of iodide, is shown to differ significantly from the observed uptake only when the turnover of iodine by the gland is very rapid.

3. The general features of the dynamic behavior of iodine in the multicompartmented system can be studied by means of an analogue computer wherein the model is represented by an electrical network. In this way the relations between specific activities in urine, in the gland, and in the extrathyroidal tissues can be studied after administra-

tion of labeled iodide. The rate constants of the various processes can be determined.

4. While the concepts developed in this chapter apply primarily to equilibrium states, with appropriate modifications and limitations they can be extrapolated into nonequilibrium situations.

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9

THE METABOLISM OF IODINE IN THE MENDOZA PATIENT

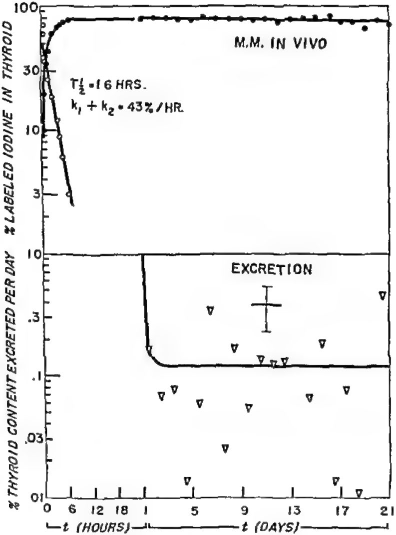
It was of primary interest to observe the metabolic fate of iodine in patients who exhibited the changes of adaptation to iodine deficiency. Seven patients with enlargements of their thyroid glands and initially rapid rates of accumulation of labeled iodine were selected for detailed study.* Measurements were made of the labeled iodine in the thyroid at frequent intervals for the first 6 hours after a tracer dose, and daily thereafter for 21 days. Twenty-four-hour urine specimens were collected throughout this period and analyzed for radioactive and stable iodide. Serum protein-bound iodine was determined in all but one patient.

Observations

Data from these seven patients are shown graphically in Figs. 26–32. The derived constants are summarized in Table X. The percentage of labeled iodine in the thyroid has been plotted against time in the upper portion of each figure. The time scale is broken to illustrate the rapid accumulation of iodine in the thyroid during the first few hours.

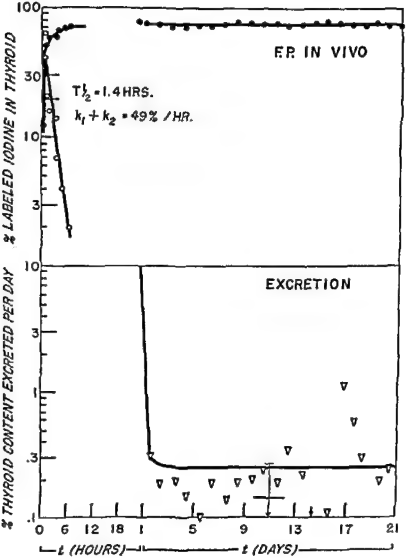
The total disposal rate of labeled iodide, $(k_1 + k_2)$, can be computed from the initial observations over the gland; k_1 is the rate constant of thyroid accumulation and k_2 that of renal excretion. The numerical value of $(k_1 + k_2)$ is computed

* An eighth patient was originally included, but since he obliged a friend by drinking his ration of Lugol's solution, all of his data are suspect and have been omitted from the discussion



content and the content at that time. From the slope of this curve

zontal bar represents the release rate calculated from the *in vivo* curve and the vertical line indicates the standard error of the rate.


100
30
10
3
% LABELED IODINE IN THYROID
F.R. IN VIVO
T½ = 1.4 HRS.
k1 + k2 = 49% / HR.
10
3
1
.3
.1
% THYROID CONTENT EXCRETED PER DAY
EXCRETION
0 6 12 18 1 5 9 13 17 21
t (HOURS)
t (DAYS)

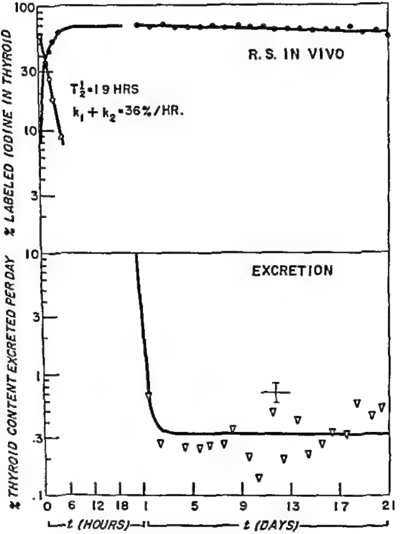


Fig 28 *In vivo* and excretion data of patient R. S. For details of plotting, see legend for Fig. 26.

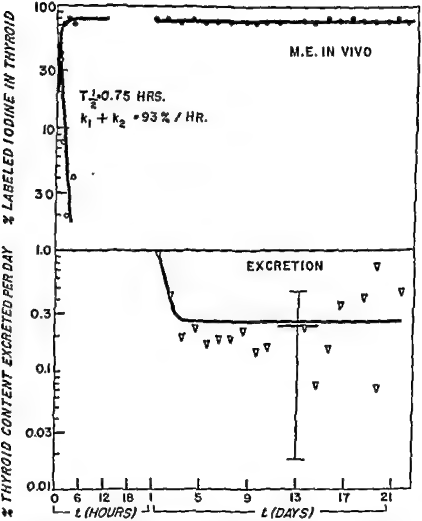


Fig. 29. *In vivo* and excretion data of patient M. E. For details of plotting, see legend for Fig 26.

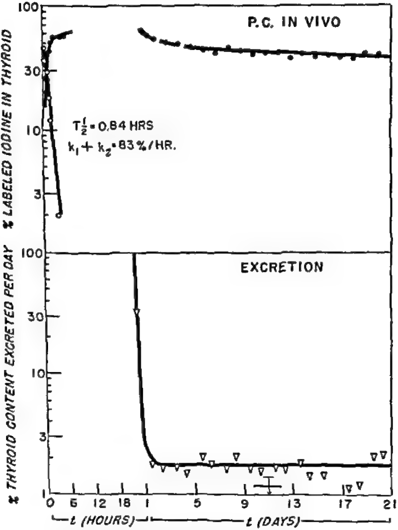


Fig 30. *In vivo* and excretion data of patient P. C For details of plotting, see legend for Fig 26 Note the rapid initial drop in the *in vivo* curve.

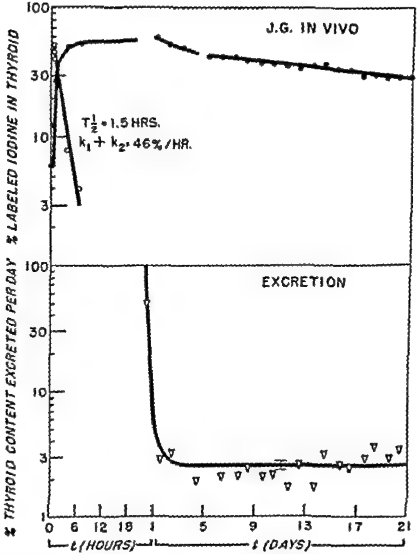
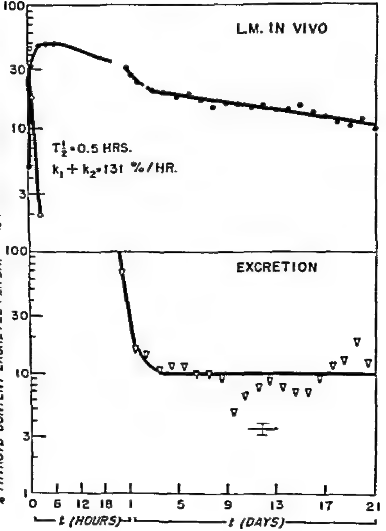


Fig. 31. *In vivo* and excretion data of patient J. G. For details of plotting, see legend for Fig. 26. Note again the rapid initial drop in the *in vivo* curve.



ting
firs
gre
in vivo curve.

TABLE X. PARAMETERS OF THYROID FUNCTION FOR SEVEN EUTHYROID PATIENTS.

Patient	Total disposal rate, $k_1 + k_1$ (%/hour)	Calculated uptake (%)	Measured uptake (%)	48-hour urinary excretion (%)	Thyroid half-time, $T\frac{1}{2}$ (days)	Effective thyroid release rate, k_4' (% of thyroid content per day)
M. M.	43	84	80 0	13 6	182 ± 72	0 38 ± 0.15
F. P.	49	86	76 7	24 9	495 ± 425	.14 ± 12
R. S.	36	81	70 3	17.9	92 ± 14	.75 ± .11
M. E.	93	93	81 4	9 4	277 ± 254	25 ± .23
P C.	83	92	62 0	22 2	61 ± 12	1.14 ± .23
J G.	46	85	58 0	31.5	27 ± 2	2.58 ± .15
L. M.	131	95	50 0 *	25 9	20 ± 2	3 46 ± .32

	Observed urinary excretion rate, E^*/Q_0^* (% of thyroid content per day)	Urinary excretion (μg/day)			Serum protein-bound iodine (μg per cent)	Thyroid iodine content, Q_0 (μg)	Thyroid iodine release rate, H (μg/day)
		Mean	Standard error of mean	Standard deviation			
M. M.	0.12	18 9	± 1.10	± 3 91	6 0, 6 5	12,600	76
F. P	.26	33 2	± 2.51	± 9.45	6.2	9,800	110
R S.	34	22 7	± 2.57	± 11 8	6.4	4,700	54
M. E.	26	10 2	± 1.44	± 6.76	3 1	3,200	45
P. C.	1 80	34 8	± 2 63	± 10.1	—	1,200	57
J. G.	2 60	43 6	± 3 02	± 12 8	6.1	974	60
L. M.	10 50	53 9	± 5.76	± 25.7	8 4	260	54

* *This value is the maximum observed uptake (at 5 hours) rather than the 24-hour uptake, which was 31.8 per cent*

graphically from the slope of the line obtained by subtracting the thyroidal content of labeled iodine during the initial hours of observation from the maximum observed uptake. This has been done for each of the seven patients. These values range from a minimum of 36 per cent of the iodide in the iodide compartment (Q_I) per hour to a maximum of 131 per cent per hour. Errors are introduced in the calculation of the disposal constants by finite rates of absorption of labeled iodide from the intestine, by delay in distribution throughout the iodide compartment, and by discrepancies between observed and true uptakes

The theoretical uptake can be calculated from the total disposal rate, $(k_1 + k_2)$, providing one assumes a value for k_2. Although renal disposal or clearance rates were not measured in these seven patients, measurements on three other patients (cf. Chapter 7) were in a range considered normal in Boston. Therefore, for the determination of theoretical uptakes, an average value of 7 per cent per hour has been assumed for k_2 [1]. The uptake is then given by Eq. (8.14),

$$U = \frac{k_1}{k_1 + k_2}.$$

The theoretical uptake depends upon estimation of the total disposal rate. Actually, the theoretical uptake is quite insensitive to changes in the total disposal rate providing this rate is large compared to the renal disposal rate.* Also,

* The relation between uptake, U, total disposal rate, $(k_1 + k_2)$, and renal disposal rate, k_2, is

$$U = \frac{k_1 + k_2 - k_2}{k_1 + k_2}. \tag{9.1}$$

To determine the effect of errors in these two parameters on the calculated uptake, partial differentials may be taken and the expression divided by U:

$$\frac{\partial U}{U} = \frac{k_2}{k_1 + k_2 - k_2}\left[\frac{\partial(k_1 + k_2)}{k_1 + k_2} - \frac{\partial k_2}{k_2}\right]. \tag{9.2}$$

If typical values of 50 per cent per hour and 7 per cent per hour are taken for $(k_1 + k_2)$ and k_2 respectively, a 20 per cent error in either parameter will produce a 3 per cent error in U.

the theoretical uptake is quite insensitive to changes in the renal disposal rate k_2, providing $(k_1 + k_2)$ is large.

Calculated values of uptake are tabulated in Table X. They range from a minimum of 81 per cent to a maximum of 95 per cent. The measured uptake is presented in the next column. Following the convention of Chapter 2, this is either the 24- or 48-hour thyroid uptake, whichever is larger.

It can be seen from Figs. 26–32 and from Table X that the *quantity* of iodine in the gland, Q_G, has an important role in determining the dynamics of iodine metabolism. The quantity Q_G has been calculated for each patient by means of Eq. (8.21), using the observed uptake. In Table X the patients have been arranged in order of decreasing thyroid iodine content. Patients M.M., F.P., R.S., and M.E. had thyroid iodine contents of 12,600, 9,800, 4,700, and 3,200 μg respectively. Over the 21-day observation period their thyroid retention curves were virtually flat. Also, the agreement between the calculated and observed uptakes is satisfactory, considering the errors inherent in both methods of estimation. By contrast, patients P.C., J.G., and L.M., who had thyroid iodine contents of 1,200, 974, and 260 μg respectively, had much larger net daily losses of labeled iodine from the glands. In addition, the patients of the latter group showed an interesting phenomenon. There was a rapid fall in the *in vivo* retention curves during the first two to four days, followed by a leveling off thereafter to an exponential curve of smaller slope (longer half period). These biphasic curves will be considered in detail later.

Decreasing values of thyroid iodine content could also be correlated with increasing divergence of the calculated and measured values of uptake. For example, the measured uptake of patient L.M., who had the smallest value for Q_G, is scarcely one-half of the calculated uptake. The most reasonable explanation of the discrepancies is that it is impossible to measure directly the fraction of labeled iodine accumulated

by the gland as hormone during the accumulation period. The *theoretical* uptake is the accumulation that would have been observed if there had been no thyroid release. The *observed* uptake fails to take account of the labeled iodine that is accumulated and secreted before the measurement is completed. The discrepancy between the two is of small moment when release rates are small, but it is important when, as in these latter three patients, the turnover of labeled iodine is rapid. Confirming this explanation is the observation that the 48-hour urinary excretion of labeled iodine, as shown in Table X, did not increase appreciably with decreasing thyroid iodine content. Presumably this labeled iodine, which was unaccounted for either in the urine or in the gland, was in the extrathyroidal pool of protein-bound iodine, where it had arrived by making a circuit through the gland before the uptake measurement was made.

After the first few days the retention curves of all seven patients appeared to be best represented by simple exponential curves, which are straight lines when plotted on a semilogarithmic scale. This straight-line relation was observed after the first 24 hours in the patients of Figs. 26–29, but only after an initial rapid drop in those of Figs. 30–32. The effective thyroid release rate, k_4', has been calculated for each of these curves by the method of least squares.* The solid lines have been fitted to the points by this method. The effective release rates in per cent per day and the retention half-times in days are presented in Table X,† together with their standard errors. The thyroid content of iodine appears

* The effective release constant, k_4', is the final observed rate of disappearance of labeled iodine from the gland It is less than the secretion rate, k_4, because of the reutilization of labeled iodine derived from the peripheral breakdown of labeled hormone If one neglects extraurinary loss of iodine, then one finds the relation

$$k_4' = k_4(1 - U).$$

† The relation between effective release rate, k_4', and half-time, $T\frac{1}{2}$, is $T\frac{1}{2} = 0.693/k_4'$.

to be directly correlated with the half-time of labeled iodine in the gland, and inversely correlated with the effective thyroid release rate expressed in per cent of gland content per day.

The observed values for the excretion of labeled iodine in the urine are plotted in the lower sections of Figs. 26–32. They are expressed as percentage of the thyroid content that is excreted per day. This quantity was calculated by dividing the percentage of the dose of labeled iodine excreted on any day by the fraction of the dose that was present in the thyroid on that day. Only the second time scale is used in plotting these data. The initial 24-hour excretion was off the scale in Figs. 26–29 and has not been plotted.

If the retention curve is a simple exponential function, the excretion curve plotted in this way should rise within the first few days and approach a constant value equal to the effective release rate from the thyroid. This assumes that the effective release rate is small and that extraurinary loss of iodine is negligible. Although in some of the patients the excretion data tend to show a slight increase following the initial rapid decline, the fluctuations in excretion in most patients preclude a quantitative analysis of the shape of the excretion curve. Therefore, a straight line has been plotted at the average excretion E^*/Q_G^* from the third to the twenty-first days. These average excretions are tabulated in Table X.

The calculated urinary excretion rate obtained from the slope of the exponential portion of the retention curve k_4' has also been plotted in Figs. 26–32, together with its standard error. It is seen that the observed rate, like the calculated excretion rate, tends to increase with decreasing thyroid iodine content, and that this rate tends to diverge from the calculated rate with decreasing thyroid iodine content.

The divergence is probably related to the method of calculation. The effective release rate was calculated from the exponential portions of the retention curves and neglects

the initial rapid loss of labeled iodine from the gland in the last three patients. Consequently, relative to the calculated effective release rate, there was a higher observed urinary excretion rate in two of the patients who showed the fast initial component of release than in those who did not.

Shape of Retention Curves

It has already been demonstrated that the magnitude of the discrepancies between calculated and measured uptakes, and between effective release rate and observed excretion rate, are roughly correlated with decreasing thyroid iodine content. The value of thyroid iodine content has been calculated from Eq. (8.21):

$$Q_G = \frac{UE}{E^*/Q_G^*}.$$

This equation neglects fecal excretion of iodine, assumes that the iodine in the thyroid is uniformly labeled, and assumes that the specific activities of the peripheral hormone pool and of the thyroid pool are equal. The values of Q_G for the seven patients have been calculated using the mean value for E for the three-week period, and the mean value for E^*/Q_G^* from the third to the twenty-first day. The spread of values of Q_G is so large that errors of measurement are negligible by comparison. The wide range of thyroid-iodine content is one of the most interesting and puzzling observations of the entire study.

The rapid initial drop in the retention curve might be explained in several ways:

1. Certain components of the gland, such as nodules, might have release rates that differ materially from those of the rest of the gland.

2. Trapped iodide might be released before becoming formed into hormone or hormone precursor.

3. A biphasic curve is expected in all patients as the hormone pool becomes labeled and thyroid reutilization of

iodide decreases the observed thyroid release. This effect will be much more evident in patients with severely depleted glands.

4. In the iodine-depleted state the thyroid iodine might be represented by two compartments with widely different release constants. One of these could be the parenchymal cells which rapidly produce hormone from labeled iodide and release it directly into the blood, and the other could be the colloid stores from which labeled hormone is mobilized much more slowly.

The first hypothesis seems most unlikely. Some of the patients with biphasic curves had glands that were diffusely hyperplastic. Also, the exceedingly rapid half-time of the first phase of the release curve was not seen in many patients with nodular glands.

The second hypothesis requires more careful consideration. Trapped but chemically unbound iodide of the thyroid gland is in equilibrium with the iodide of the blood, and returns to the blood as iodide is cleared from the blood by renal excretion. Trapped labeled iodide that leaves the gland and returns to the blood is rapidly excreted in the urine. If the rapid thyroid release rate of the first phase of the retention curves were simply due to a return of trapped iodide to the blood, then equivalent amounts of labeled iodide should have been detected in the urine. Actually, after the first or second day the excretion rate of labeled iodide was constant, or very nearly so, in spite of the fact that at these times labeled iodine was rapidly disappearing from the gland. Evidently the labeled iodine that was leaving the gland was in a form which was not readily excreted, presumably hormone.

The second hypothesis also fails if thereupon one attempts to calculate from the data of patient L.M., for example, reasonable values for hormone-secretion rate. Thus, if it is assumed that the initial rapid phase of the retention curve was unrelated to hormone formation, then the magnitude of

the true uptake could be obtained by extrapolating the logarithmic second phase of the retention curve back to zero time. This gives an uptake of between 15 and 20 per cent. The hormone-secretion rate calculated from this uptake would have the extremely low value of 9 to 13 μg of iodide per day [Eq. (4.4)]. Furthermore, if the hormone secretion rate is calculated from the observed k_4' [Eq. (8.30)], it is found either that hormone secretion rate was extremely low (12.7 to 18 μg per day depending upon whether the calculation was based on extrapolated or observed uptake), or that the value of Q_G was five times that calculated from Eq. (8.21). The quantity Q_G is almost certainly known well within a factor of 2. It would appear, therefore, that the initial rapid departure of labeled iodine from the gland is not entirely referable to simple diffusion of trapped iodide back into the blood, although this could perhaps account for part of the initial rapid fall.

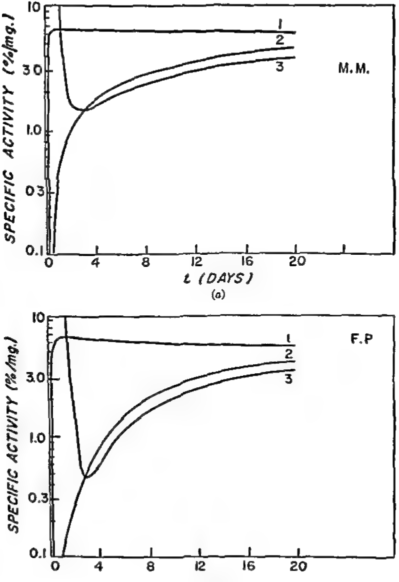
The third hypothesis can be tested by quantitative determination of the shape of the curves expected for the three-compartment thyroid model. The problem was investigated by calculating the specific-activity curves for the three compartments with the analogue computer discussed in Chapter 8 The values of the parameters are presented in Table XI. The thyroid iodine content, Q_G, is that calculated previously by Eq. (8.21) and presented in Table X. An average value of 1,200 μg of hormonal iodine is assumed for Q_B. The quantity Q_I is calculated from the observed excretion and an assumed renal disposal rate of 7 per cent per hour or 168 per cent per day.* Although estimates of H have been obtained in each of these patients as discussed in Chapter 4, an average value of 70 μg per day was assumed for all patients. The value of H for these seven patients has

TABLE XI. VALUES USED FOR COMPUTATION OF FIG 33.

Patient	Iodide, Q_I (μg)	Thyroid, Q_G (μg)	Extrathyroidal hormone, Q_B (μg)	Intake, In (μg/day)	Hormone release, H (μg/day)	Excretion, E (μg/day)
M. M.	11 3	12,600	1200	18 9	70	18 9
F. P	19 7	9800	1200	33 2	70	33 2
R S	13.5	4700	1200	22.3	70	22 3
M E	6 1	3200	1200	10.2	70	10 2
P C	20 7	1200	1200	34 8	70	34 8
J G	26 0	974	1200	43 6	70	43 6
L. M.	32 0	260	1200	53 9	70	53 9

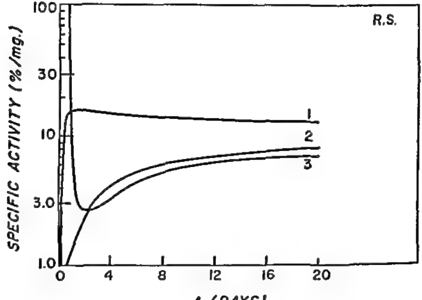
been calculated by means of Eq. (4.4), using the measured uptake (Table X). These values range from 45 to 110 μg per day. For convenience in comparing the curves, a mean value of H was preferable.

The specific-activity curves obtained from the analogue computer for the seven patients are shown in Fig. 33. The dimensions of the ordinates are per cent of the dose of labeled iodine per milligram of iodine. The total per cent in each compartment may be obtained by multiplying this value at any time by the amount of iodine in the compartment in milligrams. Curve 1 represents the specific activity of the thyroid. In each of the seven cases it shows the rapid accumulation and gradual release of iodine by the gland. Curve 2 represents the specific activity of the extrathyroidal hormone compartment. It rises smoothly and if followed for a sufficient length of time would in every case cross Curve 1 and remain somewhat higher thereafter. The graph for L.M. [Fig. 33(g)] demonstrates this feature. Curve 3 represents the specific activity of the iodide compartment. The specific activity of this compartment drops rapidly from an initial value ranging from 10 to 1000 times that of the maximum gland specific activity to a minimum value at approximately the point where it equals the extrathyroidal-hormone specific

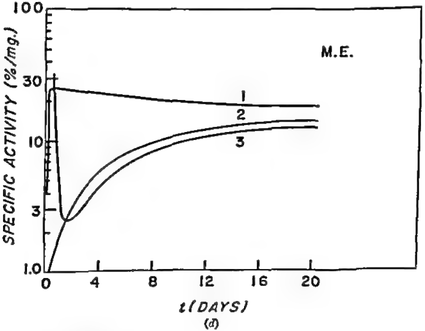


SPECIFIC ACTIVITY (%/mg.)
10
3.0
1.0
0.3
0.1
0
4
8
12
16
20
1
2
3
M.M.
t (DAYS)
(a)
SPECIFIC ACTIVITY (%/mg.)
10
3.0
1.0
0.3
0.1
0
4
8
12
16
20
1
2
3
F.P
t (DAYS)
(b)

Fig. 22. Spec [illegible]

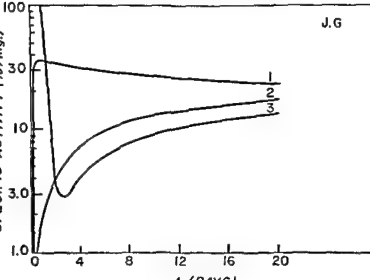


(c)

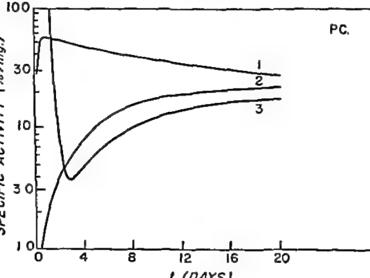


(d)

Fig. 33 (*Continued*).

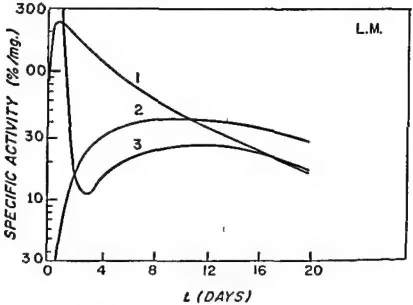


(e)



(f)

Fig. 33 (*Continued*).



(g)

Fig 33 (*Continued*).

activity (Curve 2). *Thereafter it remains somewhat lower* but similar in shape * to the hormone curve.

The only specific-activity curve that can be directly compared with the experimental data is that of the gland, Curve 1. If the values of Curve 1 are multiplied by the thyroid content, the resulting curve should equal numerically the *in vivo* curves of Figs. 26–32. Since we are primarily interested in comparing the *shapes* of the curves, we have not taken this numerical step. The *in vivo* curves of M.M., F.P., R.S., and M.E. are satisfactorily represented by the computed curves. However, the computed curves of P.C., J.G., and L.M. show increasing discrepancies from the observed curves. In the computed curves the initial steep

* The term "similar shape" means that the curves are related by a con- ... ordinate dis- ... in this way ... owering one

slope gradually approaches the final exponential slope. These are qualitatively similar to the observed curves, but there are discrepancies in magnitude and in time scale. In the observed curves the initial drop is much more pronounced and is virtually completed in four days.

The lack of agreement between the first portion of the observed retention curves and the first portion of the corresponding curves predicted by the analogue computer may be expressed in terms of the difference between the 24-hour uptake and the uptake calculated from the rate constants k_1 and k_2 by Eq. (8.14). According to the curves obtained with the analogue computer, this difference should range from 1 to about 25 per cent of the uptake calculated from the rate constants, increasing as the quantity of iodine in the thyroid decreases. But from Table X it is evident that this difference calculated from the actual observations for patients P.C., J.G., and L.M. was 33, 32, and 66 per cent of the uptake calculated from the rate constants, respectively.

The specific activity of the urine at any time is equal to the specific activity of the iodide compartment. Therefore, Curve 3 should be similar to the curve of observed urinary excretion of labeled iodine. The urinary excretion of Figs. 26–32 is plotted as per cent of thyroid content per day rather than as per cent of administered dose per day. Accordingly, in order to observe the similarity, the plotted curves of urinary excretions in Figs. 26–32 should be compared with Curve 3 divided by Curve 1. Since Curve 1, however, is very nearly constant for patients M.M., F.P., R.S., and M.E , Curve 3 can be compared directly. The observed curves of urinary excretion were not significantly different from straight lines. However, the scatter of the points could obscure a tendency to follow the shape of the corresponding Curve 3 obtained from the computer for these four patients

The observed curves of urinary excretion for patients P.G., J.G., and L.M. failed to fit the analogous curves derived from the computer. The *in vivo* curves (Curve 1) fell

much more rapidly than in the first four patients, and accordingly, the ratios of Curve 3 to Curve 1 rose much more during the first eight days. *In these patients the observed* urinary excretion rate was higher than in the first four, and consequently there was improved experimental accuracy. Contrary to expectation, the observed excretion was more nearly constant than in the first four cases.

It appears that the data from these patients are not well represented by a simple model which has a single compartment of hormone in the thyroid with a single release-rate constant. The discrepancies arise when one tries to fit the model to patients with amounts of iodine within their thyroid glands that are less than 1500 μg.

It was of interest, therefore, to choose an alternative model of thyroid function in which the iodine is considered to occupy two compartments of different magnitude and with different release constants. This is the fourth hypothesis mentioned above and is schematically represented by Fig. 34. The data of patient L.M. were selected because her *in vivo* curve of disappearance of labeled iodine from the thyroid illustrated most dramatically the biphasic curves, and because her thyroid gland contained the least amount of iodine.

The constants were arbitrary to a degree. The size of the iodide compartment was obtained from the iodide excretion and the assumed renal excretion rate of 7 per cent of the iodide compartment per hour. The conventional value of 1200 μg was chosen for the extrathyroidal hormone. The two thyroid iodine compartments were assigned values of 300 and 50 μg, and hormone secretion rates of 15 and 55 μg respectively of iodine per day were assumed.

The specific-activity curves calculated by the computer (Fig. 35) have many of the characteristics of the observed data of Fig. 32. The values of thyroid labeled iodine content divided by the thyroid iodine content have been plotted in

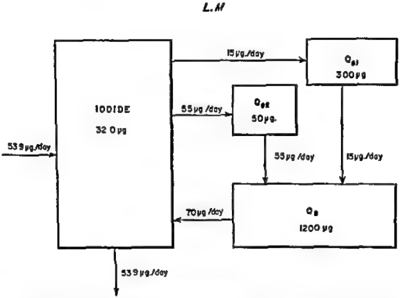


Fig. 34. Four-compartment model assumed to explain observed behavior of labeled iodine in patient L. M. The difference between this model and that represented by Fig. 24 is the second thyroid compartment Q_{G2}. For discussion of the numerical values and significance of compartments, see text. Q_{G1}, quantity of iodine in the first posited compartment of the gland, Q_{G2}, quantity of iodine in the second posited compartment, Q_B, quantity of hormonal iodine in the extrathyroidal tissues.

Fig. 35 for direct comparison. The initial rapid drop is well represented, as is the final smaller slope. The discrepancy between theoretical and observed uptake is also shown by the calculated curves. In addition, the ratio of Curve 3 to Curve 1 after four days appears to be quite similar in shape to the observed urinary excretion as plotted in Fig. 32.

These similarities neither prove nor disprove the validity of the model chosen. Any number of more complicated models could be selected to match the observed data. However, the four-compartment model appears to embody the simplest and most logical assumptions and to give good

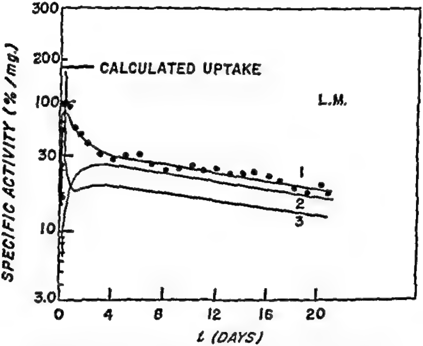


Fig. 35. Specific-activity curves for the four-compartment model of Fig. 34. For discussion of curves, see legend for Fig 33. The *in vivo* data for patient L. M., Fig. 32, divided by the thyroid content in milligrams have been plotted on this chart and the agreement between observed and calculated *in vivo* curves is seen to be good The uptake calculated from the hormone output, urinary excretion, and Q_a from Fig. 34 is also plotted.

agreement with observations. Indeed, there is a histological counterpart of the two compartments envisaged in the thyroid. The cells might be thought of as one compartment, small in volume but with rapid turnover and, therefore, relatively important in the severely depleted gland, and the colloid as another compartment, which has a larger volume and slower release rate. The dynamics of the colloid compartment would dominate any observations made of iodine release from the gland that contains an abundance of iodine.

Further information on the shape of the thyroid retention

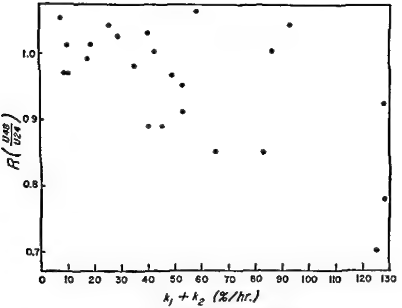


Fig. 36. The ratio of 48- to 24-hour thyroid labeled iodine plotted against the total disposal rate, $(k_1 + k_2)$, for 24 patients The correlation is seen to be poor See text.

curve was obtained from studies on other patients. In addition to the seven patients of Table X on whom estimates of $(k_1 + k_2)$ and Q_G were made, the six patients of the thyrotropin study of Chapter 10 and three patients of the iodide study of Chapter 11 also have similar data. In addition, eight other patients have estimates of the total disposal rate $(k_1 + k_2)$ To investigate the relation of the shape of the thyroid retention curve during the first 48 hours to other thyroid parameters, the ratios of the 48-hour to the 24-hour thyroid accumulation values were plotted against the total disappearance rate (Fig. 36). There appears to be a tendency for this ratio to decrease with increasing total disposal rate, and therefore increasing uptake. It will be appreciated that very small errors in uptake determinations make very large fluctuations in the ratio of 48- to 24-hour uptake.

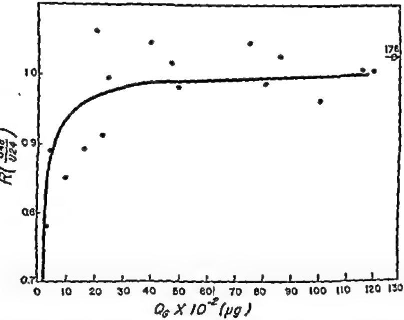


Fig. 37. The ratio of 48- to 24-hour thyroid labeled iodine plotted against the thyroid iodine Q_G for 17 patients The solid curve is the relation calculated for a hormone output, H, of 70 μg/day. The general agreement between experimental values and theory is seen to be good.

It has previously been shown that the shape of the thyroid retention curve could be correlated with the thyroid iodine content. The ratios of the 48- to 24-hour thyroid accumulations for the 17 patients who have had estimates of Q_G have been plotted against the thyroid iodine content (Fig. 37). The solid curve is the expected ratio between the 48-hour and 24-hour values, assuming a single thyroid compartment of organic iodine and a release rate of 70 μg of iodine daily. The correlation suggests that the thyroid iodine content is one of the important parameters determining the early shape of the retention curve. The agreement between plotted points and the theoretical line appears to be reasonable even for small values of Q_G. However, the full effect of the second compartment is not apparent from this ratio because much

of the turnover of the second compartment is completed before the 24-hour reading. This is particularly true in patients with very small thyroid iodine content. For example, in L.M., who had the smallest thyroid iodine content, 260 μg, the ratio between the 24-hour uptake and the highest observed uptake was 0.64.

Summary

1. The retention and disposal of iodide were observed for periods of three weeks in each of seven patients. The thyroidal content of iodine varied from 260 to 12,600 μg.

2. The observed thyroid retention curves and excretion curves are consistent with the usual three-compartment model of iodine metabolism for those patients with thyroid iodine contents above 1500 μg.

3. When the thyroidal content was below 1500 μg, the observed data were inconsistent with predictions from the three compartment model. The shapes of the *in vivo* disposal curves, the calculated uptakes, the urinary iodine excretion rates, and the slopes of the excretion curves failed to fit the model.

4. A model employing two thyroid compartments, each with its own release constant, appears to be consistent with the observed results. These two compartments may be the cells and the colloid, the former being "seen" when the iodine content of the whole gland is low.

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10

THE EFFECTS OF METHIMAZOLE AND THYROTROPIN

The metabolism of iodine is profoundly influenced by the antithyroid drugs of the thioamide group [1] and by the thyrotropic hormone of the anterior pituitary gland [2, 10]. One of the most potent of the antithyroid drugs that has found clinical usefulness is 1-methyl-2-mercaptoimidazole, or methimazole [3]. Drugs of this group affect the thyroid gland by preventing the incorporation of iodide that has been trapped by the gland into chemical combination with tyrosyl groups. In this way hormone synthesis is inhibited [7]. Thyrotropic hormone, on the other hand, appears to stimulate all phases of thyroid activity [2, 4].

The observations now to be described are concerned with the effects of methimazole and of thyrotropic hormone upon the metabolism of iodine by six Mendoza patients. The design of this experiment was similar to that of Goldsmith *et al.* [2] in their studies of thyrotoxic patients. Throughout the experiment measurements identical with those of the previous chapter were made of the retention of labeled iodide and excretion of both iodide and labeled iodide. After one week of control observations, each patient received methimazole daily for approximately two weeks. After a week of the antithyroid drug, thyrotropin was administered twice daily for several days. Finally, just before the methimazole was discontinued and two to three days after the cessation of

thyrotropin, the effectiveness of the drug in blocking hormone synthesis was tested with a second tracer of labeled iodine.

Six patients who had initially rapid accumulation rates of labeled iodine in their thyroid glands were chosen for these studies. Each was clinically euthyroid and had a normal serum protein-bound iodine concentration. The data are presented in Figs. 38–49 and in Tables XII–XVI. The even-numbered figures give the *in vivo* data for the retention of labeled iodine, while the odd-numbered figures give the urinary excretion rates of labeled iodide and iodide for the patients of the immediately preceding even-numbered figures. Excretion rates for iodide and labeled iodide are plotted as per cent of thyroid content per day.

Control Period (I)

The quantity of labeled iodine in the thyroid was observed frequently during the first 5 to 6 hours of the control period, and daily thereafter. From the initial observations the total disposal rate, $(k_1 + k_2)$, was computed. The values ranged from 23 to 87 per cent per hour. The uptakes calculated from these rates and from an assumed value of 7 per cent per hour for k_2 by means of Eq (8.14) are also shown in Table XII. There is satisfactory agreement between the calculated and the observed uptakes in all instances except A. Mır., and even in that instance the discrepancy is not so large as for some of the patients of the previous chapter. It will be recalled that the discrepancies between observed and calculated uptakes were large for patients who had less than 1500 μg of iodine in their thyroid glands. The quantity of iodine in the glands of the six patients of the present group ranged from 1820 to 17,600 μg. In the table the patients have been arranged in order of decreasing thyroid iodine content, Q_G.

The percentage of the administered dose of labeled iodine

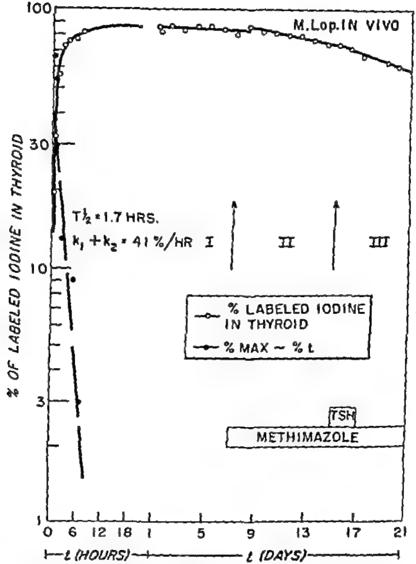

Fig. 38. *In vivo* data for patient M. Lop. The rapid accumulation of labeled iodine is plotted on the first time scale. The total disposal rate, $(k_1 + k_2)$, is calculated as discussed in the legend of Fig. 16 Observations were taken over period I with no medication to establish the control [illegible] Methimazole was administered to the patient over periods II

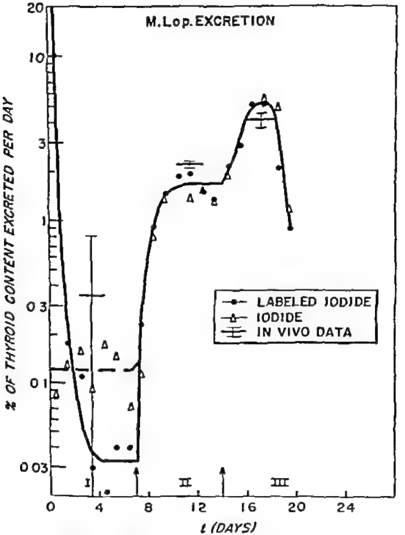

Fig. 39. Excretion data for iodide and labeled iodide for patient M. Lop. plotted as per cent of thyroid content excreted in the urine per day. The periods correspond to those of Fig. 38. During the control period,

content, Q_G. The two curves are seen to superimpose through period III. The immediate change in excretion rate following methimazole is obvious and the slower increase in excretion rate following thyrotropin is also clear. The *in vivo* release rate and its standard error obtained from the least is of Fig. 38 are plotted at the midpoint of each

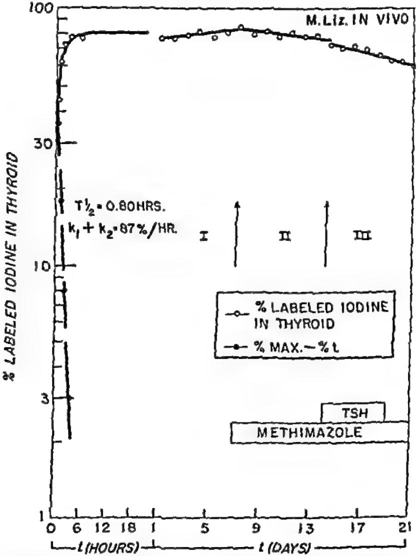

Fig. 40. In vivo data for patient M. Liz For details of plotting, see legend for Fig. 38. Thyrotropin (TSH) was given to this patient *for 5 days.*

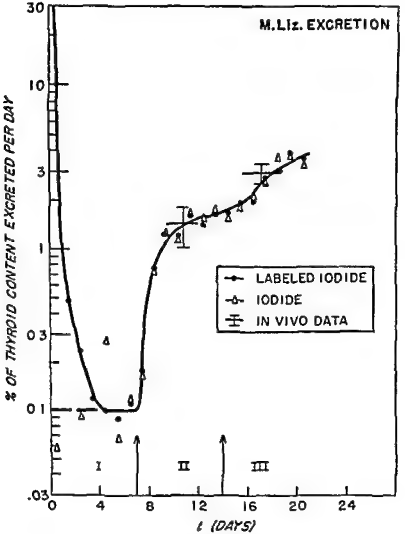

Fig 41. Excretion data for patient M. Liz. For details of plotting, see legend for Fig 39.

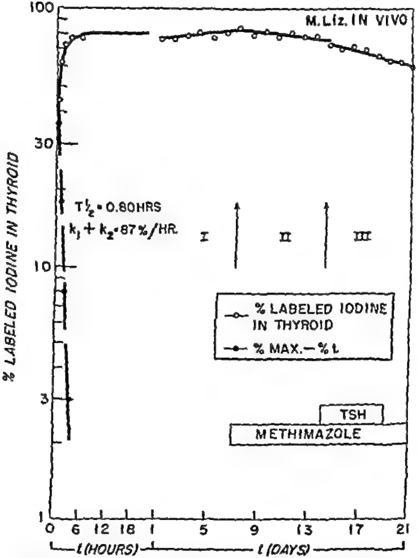

Fig. 40. *In vivo* data for patient M. Liz. For details of plotting, see legend for Fig. 38. Thyrotropin (TSH) was given to this patient for 5 days.

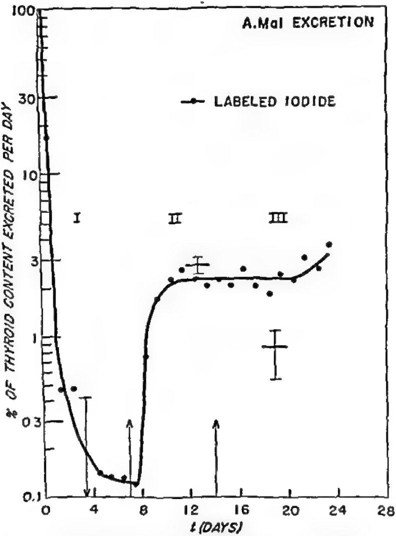

Fig 43 Excretion data for patient A. Mal. For details of plotting, see legend for Fig 39. Only labeled-iodide data are plotted because of ingestion of large amounts of iodide.

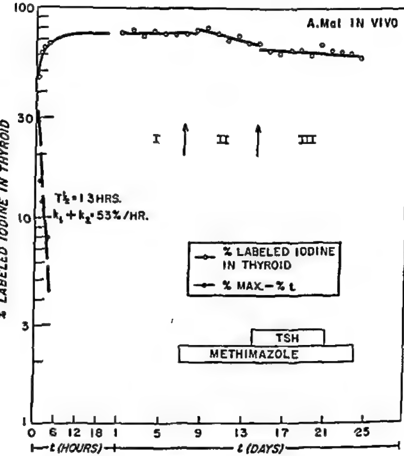

Fig. 42. *In vivo* data for patient A Mal. For details of plotting, see legend for Fig. 38. The unusual shape of the curves was undoubtedly related to ingestion of large and unknown amounts of iodide over periods II and III.

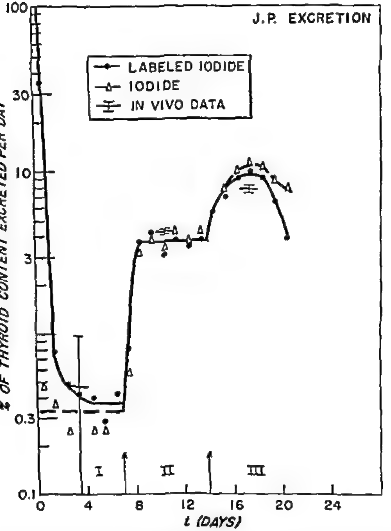

Fig 45 Excretion data for patient J P For details of plotting, see legend for Fig. 39. Note the slight divergence of the labeled iodide and iodide curves during period III.

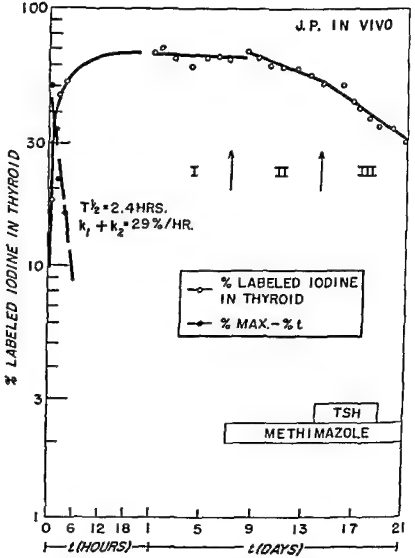

Fig. 44. *In vivo* data for patient J. P. For details of plotting, see legend for Fig. 38 Thyrotropin (TSH) was administered for 5 days.

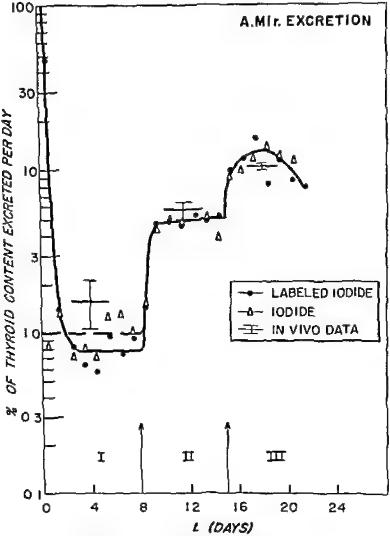

Fig 47 Excretion data for patient A. Mir. For details of plotting, see legend for Fig 39

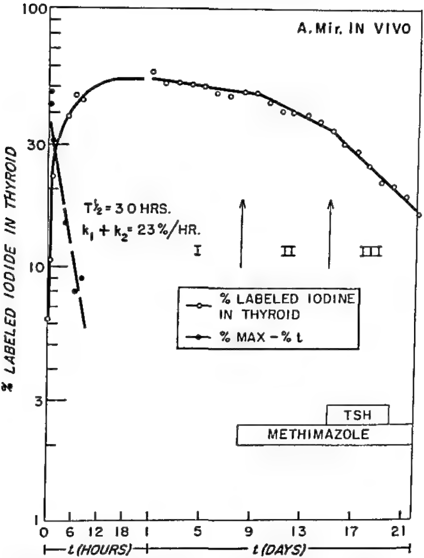

Fig 46. *In vivo* data for patient A. Mir. For details of plotting, see legend for Fig 38.

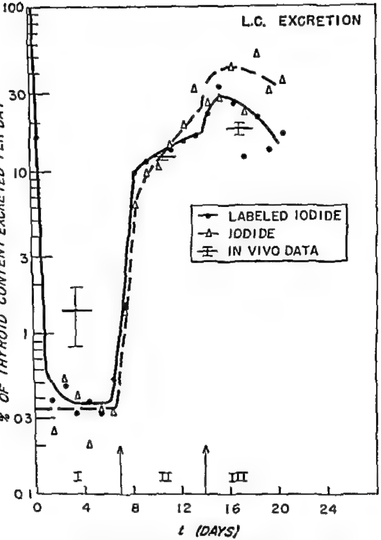

Fig. 49 Excretion data for patient L. C. For details of plotting, see legend for Fig 39 Note the large divergence of the iodide and labeled iodide curves during period III. At the end of period III, the thyroid iodine content was less than 15 per cent of that at the beginning of period II.

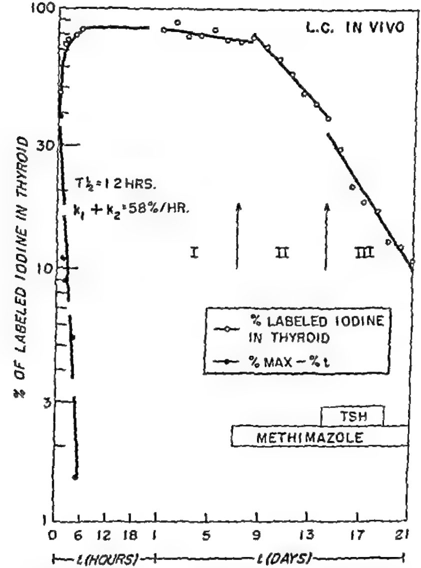

Fig. 48. *In vivo* data for patient L. C. For details of plotting, see legend for Fig. 38. Note the increased release rates resulting from a smaller thyroid iodine content.

TABLE XIII. OBSERVED HALF-TIMES AND NET RELEASE RATES FOR THREE PERIODS.

Patient	Period I, Control		Period II, Methimazole		Period III, Methimazole and Thyrotropin	
	$T\frac{1}{2}$ (days)	k_4' (%/day)	$T\frac{1}{2}$ (days)	k_4' (%/day)	$T\frac{1}{2}$ (days)	k_4' (%/day)
M. Lop.	198 ± 260	0.35 ± 0.46	31.8 ± 1.4	2.18 ± 0.10	17.3 ± 1.2	4.01 ± 0.28
M. Liz.	——	− 1.31 ± 0.33	48.5 ± 13.5	1.43 ± 0.40	23.8 ± 3.3	2.01 ± 0.40
A. Mal.	——	− 0.09 ± 0.51	25.0 ± 5.6	2.76 ± 0.61	70.5 ± 29.0	0.87 ± 0.32
J. P.	148 ± 164	0.47 ± 0.52	16.2 ± 0.5	4.26 ± 0.14	8.9 ± 0.45	7.83 ± 0.40
A. Mir	44 ± 14	1.58 ± 0.52	12.1 ± 1.3	5.72 ± 0.61	6.6 ± 0.3	10.43 ± 0.46
L. C.	50 ± 20	1.40 ± 0.56	5.7 ± 0.2	12.11 ± 0.46	3.8 ± 0.3	17.99 ± 1.47

TABLE XII PARAMETERS OF THYROID FUNCTION OF SIX PATIENTS OF THE METHIMAZOLE-THYROTROPIN STUDY.

Patient	Thyroid content, Q_G (μg)	Total disposal rate, $k_1 + k_2$ (%/hour)	Calculated theoretical uptake (per cent)	Observed uptake (per cent)	48-hour labeled-iodide excretion (per cent)	Mean iodide excretion (μg/day)
M. Lop.	17,600	41	83	87.3	8.8	24.1
M. Liz.	11,900	87	92	82.0	8.2	12.5
A. Mal.	7440	53	87	79.7	13.3	7.9
J. P.	5670	29	76	70.2	24.6	21.3
A. Mir.	2270	23	70	57.4	27.8	26.4
L. C.	1820	58	88	88.8	12.1	8.9

that was present in the thyroid of each patient was measured daily beginning with the first day. The observed release rates, k_4', are shown in Table XIII. The points of each control period were fitted to a simple exponential function, $e^{-k_4't}$, by a least-squares analysis. The net thyroidal release rate, k_4', was obtained from the slopes of these lines. The standard deviation of the slope is high compared with the slope itself for the control segment because of the long biological half-period and the short duration of the control period of observation (7 days). However, changes in slopes during the subsequent periods were of such magnitude that the changes could be shown to have statistical validity. Two of the subjects actually had slightly negative rate constants during the control phase.

The charts of urinary excretion include the measurements both of iodide and of labeled iodide in the urine. The labeled-iodide curve was obtained by dividing the percentage of the administered dose of labeled iodine excreted per day by the percentage of the administered dose that was present in the gland on that day. Similarly, the urinary-iodide curve was obtained by dividing the daily excretion of iodide by the quantity of iodine in the thyroid. The calculation of Q_G is discussed in the next section. During the methimazole period

In all of the *in vivo* curves there was a well-marked downward inflection from the beginning of the second period. The slopes of the curves again were obtained from a least-squares matching to a simple exponential function. Because of this method of curve fitting, it would not be expected that the curves for the first and second periods would join smoothly in all cases. In the least-squares analysis, the observations on the seventh day are included as the final point of the control segment and as the initial point of period II.

The net thyroid release rates, k_4', and their standard errors are given in Table XIII. These rates ranged from 1.43 to 12.11 per cent per day, corresponding to a range of half-times from 48.5 to 5.7 days. In Table XIV are shown the differences between the calculated rate constants for net release during and before the block. The differences are in all cases greater than three and one-half times their standard errors. Thus the changes in slope were significant at a 99 per cent level of confidence ($P < 0.01$). The absolute values of the differences tended to increase with decreasing thyroid iodine content. The ratios of $k_4'(\mathrm{II})$ to $k_4'(\mathrm{I})$ are given in Table XIV. The large percentage error of the release constants of the control periods makes the ratios uncertain.

TABLE XIV. DIFFERENCES AND RATIOS OF RATE CONSTANTS

Patient	$k_4'(\mathrm{II}) - k_4'(\mathrm{I})$ (%/day)	$\frac{k_4'(\mathrm{II})}{k_4'(\mathrm{I})}$	$k_4'(\mathrm{III}) - k_4'(\mathrm{II})$ (%/day)	$\frac{k_4'(\mathrm{III})}{k_4'(\mathrm{II})}$
M. Lop	1.83 ± 0.47	6.2 ± 7.9	1.83 ± 0.30	1.84 ± 0.15
M. Liz	2.74 ± 0.52	-1.1 ± 0.4	1.48 ± 0.57	2.04 ± 0.64
A. Mal	2.85 ± 0.79	-30.6 ± 173.0	-1.89 ± 0.69	0.31 ± 0.12
J. P.	3.79 ± 0.54	9.1 ± 10.1	3.57 ± 0.43	1.84 ± 0.11
A. Mir.	4.14 ± 0.80	3.6 ± 1.2	4.71 ± 0.76	1.83 ± 0.08
L. C.	10.71 ± 0.72	8.7 ± 3.5	5.88 ± 1.54	1.49 ± 0.13

The urinary excretions of labeled iodide and of iodide during period II are presented in Figs. 39, 41, 43, 45, 47, and 49. The excretion of both labeled iodide and iodide in-

the content of iodine, $(Q_G)_{bl}$, fell as a consequence of the block, (bl). The quantity $(Q_G)_{bl}$ was calculated after the seventh day from the ratio of thyroidal content of labeled iodine during the block, $(Q_G^*)_{bl}$, to that at the end of the control period, $(Q_G^*)_7$, thus:

$$(Q_G)_{bl} = Q_G \frac{(Q_G^*)_{bl}}{(Q_G^*)_7}. \qquad (10.1)$$

After the initial clearance of labeled iodide, the urinary-excretion curves for labeled iodine and iodine are quite similar during the control periods. Actually, they should not be identical because of the daily increment of dietary iodide, which for these patients was quite small, as shown in Table XII. By suitable rearrangement of the first and last terms of Eq. (8.20), it can be shown that the ratio of the labeled-iodide curve, (E^*/Q_G^*), to the iodide curve, (E/Q_G), during the control period should equal the fractional uptake, U, when the excretions of labeled iodide and of iodide are in constant ratio (secular equilibrium). Since the control periods were insufficiently long for attainment of secular equilibrium, theory cannot be tested by calculating U from these data.

The iodide-excretion data are not plotted for patient A. Mal. This patient inadvertently received large doses of iodide during the experiment. This fact was not disclosed until several months later, when it was found that suddenly in the middle of the experiment his daily excretion of iodide jumped to several milligrams daily. All his measurements therefore are suspect.

Methimazole Period (II)

Immediately after the measurement of the *in vivo* retention on the seventh day, each patient began to receive methimazole in doses of 30 mg every 8 hours. This medication was continued until the end of the experiment two weeks later.

which they were being excreted in the urine. These mean disappearance rates calculated from the slopes of the segments of the *in vivo* curves are represented by bars in the excretion charts, Figs. 39, 41, 43, 45, 47, and 49, and their standard errors by the vertical lines. The computed excretion rates seem to agree well with the observed excretion rates.

The obvious explanation for the increased net release rates of labeled iodine from the glands and the increased excretion rates of labeled iodide and iodide in the urine is that reutilization of iodide released by degradation of hormone by the peripheral tissues was prevented by the methimazole. However, there are substantial arguments which indicate that this was not the only process which was operating. If block of reutilization of iodide released in the periphery were the only process, the thyroid release rate and urinary excretion after the block should be increased by a factor of $1/(1 - U)$ [cf. Eq. (8.29)]. This ratio, obtained from the calculated uptake, ranges from 2.3 for A. Mir. to 8.9 for L.C. Surprisingly enough, the observed increases of urinary excretion of labeled iodine after methimazole ranged from a factor 5 for A. Mir. to 35 for L.C.

This discrepancy is further emphasized by calculation of the daily thyroid iodine release, H, during the two periods, as shown in Table XV. Two methods of calculation were employed. In method A, H was calculated during the control period by Eq. (4.4), and during the block by Eq. (8.28). This method is based upon measurement of uptake and iodide excretion and is independent of measurements of renal excretion of labeled iodide and thyroid content of iodine. In method B, H was calculated during the control period by Eq. (8.31) and during the block by Eq. (8.33). This method is based upon the thyroid content of iodine estimated by Eq. (10.3), the rate of excretion of labeled iodine, and the uptake.

creased sharply in all patients when the methimazole was begun. The magnitude of the change was sufficient to make a statistical study unnecessary. The excretion rates of both are in per cent of thyroid content per day. From Table XII it is seen that the excretion of iodide during the control period (and hence the iodide intake) was very small. The excretions of iodide during the methimazole periods were so high that the intake of iodide can be neglected for all practical purposes.

The thyroid content of iodine, Q_G, can be derived from the curves of excretion of iodide and labeled iodide. If it is assumed that organic binding of iodide is reduced to zero by the methimazole, the labeled iodide and iodide appearing in the urine, neglecting the small iodide intake, may be considered as derived from the hormone pool, which in turn is derived from the gland. The assumption appeared to be warranted when at the end of the experiment it was shown that methimazole in the dose schedule prescribed almost completely prevented the synthesis of hormone (Table XVI, last column). Under these conditions the thyroid specific activity will be constant and equal to that of the urinary iodide Thus

$$\left[\frac{E^*}{E}\right]_{bI} = \left[\frac{Q_G^*}{Q_G}\right]_{bI} = \left[\frac{Q_G^*}{Q_G}\right]_{7}; \qquad (10.2)$$

E_{bI}^*, $(Q_G^*)_7$, and E_{bI} are measured, and

$$(Q_G)_7 = \left[\frac{E}{E^*}\right]_{bI}[Q_G^*]_7. \qquad (10.3)$$

This calculation does not depend upon uptake as did the method of Eq. (8.21). Calculations of Q_G for these patients by Eq. (8.21) cannot be accurately made because secular *equilibrium had probably not been reached* by the end of the control periods.

The rates at which labeled iodide and iodide were disappearing from the thyroid should be the same as the rates at

increased rate of secretion of thyroid hormone. However, there was no significant difference between the protein-bound iodine concentrations at the end of the methimazole periods and the control values. Furthermore, if the excess iodine were released as hormone it would take several days for the excretion of iodide and labeled iodide to reach their new levels. The changes in slopes and excretion rates were observed to occur almost immediately after the methimazole regime was begun, and the new rates were maintained with impressive constancy for the succeeding seven days.

An alternative explanation for the discrepancies is that methimazole in some way causes iodide to be released directly from the thyroid, thereby accounting for release of labeled iodine in excess of that released as hormone. Roche *et al.* [8] have recently described a deiodinase present in the thyroid gland which removes iodide from iodinated tyrosine. The precise physiological role of this enzyme is not yet clear. It fails to deiodinate tri- and tetraiodothyronine. It releases iodine within the thyroid cell as iodide. Under ordinary circumstances this iodide should be available for reutilization in the formation of hormone. The term "recycling" has been applied to this process. However, in the presence of methimazole the iodide released by the enzyme would not be available for reïncorporation into tyrosyl groups, but would diffuse from the cells into the blood and be lost from the gland. It seems reasonable, therefore, to suppose that the loss of iodine from the methimazole-blocked gland beyond that attributable to secretion of hormonal iodine might be ascribed to inhibition of reutilization of iodide derived from deiodination of mono- and diiodotyrosine by Roche's enzyme.

Thyrotropin Period (III)

After the two weeks of observations already described, each patient began receiving 15 mg of a potent preparation

TABLE XV. LABELED-IODINE RELEASE RATES AND RATIOS.

Patient	Thyroid iodine release during control Period (I)		Thyroid iodine release during methimazole Period (II)		Ratio, II/I	
	A * (μg/day)	*B* * (μg/day)	*A* * (μg/day)	*B* * (μg/day)	*A* *	*B* *
M. Lop.	148	101	258	284	1.75	2 82
M. Laz.	126	146	160	156	1.27	1.07
A. Mal.	53	74	—	163	—	2.20
J. P.	68	97	201	206	2 96	2 12
A. Mir.	62	61	93	112	1.50	1.84
L. C.	65	61	263	256	4 04	3 94
				Mean	2 30	2.36

* Two methods of calculation, discussed in text.

During the control period the rate of hormone secretion ranged from 53 to 148 μg daily calculated by method A and from 61 to 146 μg daily calculated by method B. This spread is consistent with the observations of Chapter 4. If the pharmacological action of methimazole is simply to block the uptake of iodide for hormone synthesis, the rate of secretion of hormone should remain constant during the block. However, the observed rates of loss of iodine from the gland during the block ranged from 93 to 263 μg per day calculated by method A and from 112 to 284 μg per day calculated by method B. This corresponds to an average increase in iodine release from the thyroid during the methimazole period for five of the six patients calculated by method A by a factor of 2.30 and for the six patients calculated by method B by a factor of 2.36.

How, then, can one explain why after methimazole there was a larger than predicted increase in the excretion of labeled iodide and of iodide, and why there were unusually high values for H calculated during the methimazole period? Two explanations may be invoked. The observed increase in the rate of loss of iodine from the gland might be due to an

has an appreciable half-time of metabolic degradation [6]. In general, the curves did not reach a plateau during the short period of administration of thyrotropic hormone.

Release rates computed from the slopes of the *in vivo* segments have been plotted on the excretion charts (Figs. 39, 41, 43, 45, 47, and 49) as in periods I and II. The values agree well with the means of the observed excretion curves. In three of five curves the labeled iodide and the iodide excretions follow together closely through the third period. In two others moderate divergence was observed, although the two curves were similar. The divergences, which occurred in patients with relatively small quantities of iodine in their glands, undoubtedly arose from nonuniform labeling of the thyroid which became apparent in glands as they became severely depleted of iodine during the methimazole block.

The diminished rate of release of labeled iodine by the gland of patient A. Mal. was unique. The curves for all five of the other patients of this group exhibited downward deflections when thyrotropin was given, and the four patients of Chapter 11 also had downward deflections when they were given large daily doses of potassium iodide. Patient A. Mal. was the only subject who received both methimazole *and* iodide. The deflection upward may have resulted from a dilution of the labeled iodine in the gland because of an incomplete block by the methimazole, thereby masking an unchanged or even enhanced release of labeled iodine.

Completeness of Block

The completeness with which organic binding of iodine was inhibited by the methimazole was tested in each of the six patients by giving a tracer dose of labeled iodide after the thyrotropin had been discontinued but while each patient continued to receive 30 mg of methimazole every 8 hours. After the 24- and 48-hour uptakes were measured, 2 ml

of thyrotropic hormone * every 12 hours by the intramuscular route. The administration was continued for five days in all except M. Lop. Administration to this patient was discontinued after three days when she developed a severe reaction (*v.i.*).

The administration of thyrotropin was accompanied by a further increase in the net release of labeled iodine from the gland in each patient except A. Mal. This patient suddenly began excreting between 1 and 3 mg of iodide at the midpoint of the methimazole period, and continued to do so until the end of the thyrotropin period. The release rates, k_4', during period III are shown in Table XIII. The slopes again were fitted by least squares. The differences between the net release rates of period III and period II are given in Table XIV. The changes in release rates are all significant at the 95 per cent level of confidence. The ratios of k_4'(III) to k_4'(II) are independent of the thyroid content of iodine and except for A. Mal. have a value of about 1.8 for this dose of thyrotropin. To put it differently, the thyroids were releasing iodine at nearly twice the previous rate. These rates refer to percentage of total labeled iodine in the gland released per day. They are not absolute release rates. In three patients there were slight rises in serum protein-bound iodine after the thyrotropin was begun. In one there was no change, and in two, appropriate blood samples were not obtained.

The excretion curves of labeled iodide and of iodide showed definite increases in rates during administration of thyrotropin, but during thyrotropin the rises were slower and the changes in excretion were smaller than with methimazole alone. The slower rise is expected from the fact that some of the excreted iodide derives from secreted hormone which

* The thyrotropin was furnished by Armour and Co of Chicago, Illinois. Each vial contained 30 mg of Lot K-39405R purified thyrotropic hormone (3 Evans units per mg). There was less than 1 unit of posterior pituitary present, and other hormones were absent.

due to the intensive therapy with thyrotropic hormone. This substance is well known to expand the iodide space of the gland [9].

Reactions to Thyrotropin

In each of the six patients there was a sudden reaction of pain, tenderness, and swelling of the thyroid gland which began two or three days after the injections of thyrotropin were begun. In M. Lop. the reaction, accompanied by fever and vomiting, was so severe that administration of the hormone had to be discontinued. In the most striking instances the glands were doubled in size, but in others the increase was hardly appreciable. The skin over the glands was distinctly warm, and the glands themselves became more firm and were very tender to palpation. Except for the patient who had fever and vomiting, the findings were confined to the thyroid. It seems reasonable, therefore, to suppose that the disorder was a reaction of the thyroid gland itself to the thyrotropic hormone. The findings suggested a sudden increase in hypertrophy and particularly in vascularity.

In the patient with the severe reaction, the gland returned to its previous size within about three days. In the other patients the tenderness subsided within about three days, in spite of continued administration of thyrotropin.

The Quantity of Iodine in the Thyroid Gland

From Tables X and XII it can be seen that there were very wide variations indeed in the quantity of iodine sequestered in the glands of these patients. The variations were so wide and the larger quantities so unexpectedly large that a detailed consideration of this problem is in order.

The computation of the quantity Q_G for the patients of Chapter 9 depends upon estimates of uptake, U, average

of a solution of potassium iodide containing 300 mg of iodide per milliliter was given to all but one subject. It was assumed that labeled iodine present in the gland three hours later was in chemical combination and not in equilibrium with the iodide compartment. The results of these studies are shown in Table XVI. Appropriate corrections were made for the

TABLE XVI CONTROL UPTAKE, UPTAKE DURING METHIMAZOLE, AND PER CENT OF OBSERVED TRACER *PRESENT IN THE THYROID 3 HOURS AFTER* ADMINISTRATION OF IODIDE.

Patient	Initial uptake (per cent)		Methimazole uptake (per cent)		Thyroid content 3 hr after KI (per cent)
	24-hr	48-hr	24-hr	48-hr	
M Lop.	85 5	87.3	17.7	11.2	——
M Liz.	77.0	76 9	53 2	42 2	10 3
A. Mal	76.7	79 6	42.0	26.2	4 6
J. P.	68 5	70 2	19 2	13.1	10 7
A. Mir	57.4	52 1	10 8	4.8	2 6
L. C.	83 4	88 8	19.9	10 2	9.1

labeled iodine already present in the gland from the tracer dose given three weeks previously.

One-fifth to one-half of the labeled iodine in the thyroid disappeared between the 24-hour and the 48-hour readings. A surprising portion of the tracer dose was retained by two of the glands even after 48 hours. Evidently, these two glands had a very large iodide space since most of the labeled iodide from the new tracer was lost when the iodide space was flooded with iodide.

Retention of iodide after 24 and 48 hours was much higher than in any of the eight patients of the methimazole study of Chapter 7, except for one who was receiving only 5 mg of methimazole every 8 hours and omitted the first tablet after the tracer dose. The unusually expanded iodide spaces and the consequent slow rate at which the labeled iodide left the iodide space of the gland and was excreted may have been

there might be a residual component of thyroid iodine which could not be so readily mobilized as the rest.

In seeking an explanation for the anomaly, it must be remembered that the rate of hormone synthesis does not always equal the rate of hormone secretion. In the face of a persistent and severe dietary deficiency of iodine, the ability of the thyroid gland to compensate by increasing its reutilization of iodide released during the metabolism of thyroxine in the tissues may not be sufficient to prevent a negative iodine balance. Despite a high uptake, the hypertrophied gland secretes more iodine as hormone than it can collect as iodide and the stores of hormone in the colloid approach exhaustion. If the supply of iodide to such an enlarged but depleted gland is increased, the negative iodine balance may suddenly be replaced by a positive iodine balance as the persisting high uptake enables the gland to recoup some of its losses. In Chapter 5 it was shown that an elevated uptake may persist despite the accumulation and storage of several milligrams of organic iodine. It seems possible that the large amounts of iodine calculated to be present in the thyroid glands of some of the patients may simply be an inheritance from a previous period of relative iodine abundance. It may be that as long as the iodine *concentration* in the gland is subnormal, an increased secretion of thyrotropic hormone is required to maintain a normal rate of secretion of thyroid hormone, and, incidentally, a continued high uptake. This sequence of events is strongly reminiscent of the repeated cycles of depletion and repletion postulated by Marine [5] as an explanation for the colloid-filled gland which may be an end result of endemic goiter. Whatever the explanation, the wide range of values for Q_G remains as one of the most puzzling and challenging observations of the entire study.

Summary

1. The retention and disposal of iodide and of labeled iodide were observed in six patients during three periods of

daily excretion of iodide, E, the average daily excretion of labeled iodide, E^*, and the quantity of labeled iodine in the gland from day to day Q_G^*. The maximum error in the estimation of U is certainly no more than 20 per cent, and is considerably less for patients with high values of Q_G, where biphasic retention curves were not seen. The values for E and E^* are probably known within 20 per cent, and Q_G^* is known within 10 per cent. The maximum error, therefore, with which Q_G is known is certainly no more than a factor of 2, and is probably considerably less.

The computation of the quantity Q_G for the patients of the present chapter depends upon estimates of E_{bl}, $(Q_G^*)_1$, and E_{bl}^*, and is independent of U. Because E_{bl}^* was large during the methimazole period, Q_G is perhaps more accurately known for these six patients than for the eight of the preceding chapter. It seems probable that the maximum error with which Q_G is known for this group is no more than a factor of 2, and it is probably much less.

Granting errors of a factor of 2 in the computation, there still appears to have been a very wide range of values for Q_G. Patient L.M. had a calculated 260 μg, whereas patient M. Liz. had a calculated 17,600 μg of iodine in the thyroid gland.

It seems anomalous that glands containing many milligrams of iodine should continue to extract iodide from the blood at rates which are sufficiently high to guarantee maintenance of hormone stores in excess of those of patients living in areas of iodide abundance, while others with comparable avidity for iodide become severely depleted of iodine. It should be remembered that Q_G is the total quantity of iodine in the gland, and that these glands were large. The concentration of iodine per unit weight of gland, therefore, may have been much smaller than that of the normal thyroid gland. Nevertheless, the data suggest that the retained iodine was largely available for secretion. Only after methimazole and thyrotropin was there evidence that

of endemic goiter," *Comptes-Rendus de la Conférence Internationale du Goitre* (Hans Huber, Berne, 1928), pp. 68–82.

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observation. The first was a control period. During the second and third periods, methimazole was given. During the third period each patient received daily injections of thyrotropin.

2. When methimazole was given, there was an increase in the release of labeled iodine from the thyroid and a rise in the urinary excretion rate of iodide and of labeled iodide. The increases were in considerable excess of those anticipated if the sole action of methimazole is to inhibit reutilization of the iodide from hormone degradation. A possible explanation for this observation is offered.

3. Administration of thyrotropin caused a further increase in release of labeled iodine and increases in urinary excretion rates of iodide and labeled iodide, but the latter rates tended to diverge in some of the patients, suggesting a residual component of thyroid iodine which was mobilized with difficulty.

4. All subjects had a transient episode of pain, swelling, and tenderness of the thyroid gland when thyrotropin was given.

5. The puzzling finding of wide variations of thyroid iodine content is discussed.

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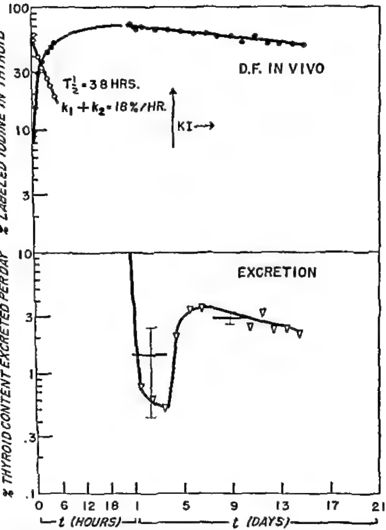

Fig. 50. The effect of iodide on the metabolism of labeled iodine. Potas- [illegible]
[illegible]
[illegible]
in the urine The *in vivo* release rate and its standard error obtained from the least-squares analysis of the upper curve is plotted at the midpoint of each segment. The subject was a 37-year-old female with a nodular goiter estimated to weigh approximately 80 gm.

11

THE EFFECT OF LARGE DOSES OF IODIDE ON THE METABOLISM OF IODINE

The data of Chapter 5 provide information concerning the effects of graded doses of iodide on the net retention of iodine by the body, and of larger doses of iodide on the uptake of iodine by the thyroid gland. These data disclose nothing of the influence of large supplementary doses of iodine on the metabolism of previously stored iodide. The effect of iodide on iodine metabolism is of importance because of the widespread use of relatively large doses of iodine in clinical therapeutics.

Observations

Four patients who were given tracer doses of labeled iodine were observed over a control period of from four to nine days while frequent measurements were made of the retention of labeled iodine in the thyroid gland and excretion of labeled iodide and iodide in the urine. In three of the four patients, measurements immediately after the administration of labeled iodine allowed estimates of the total disposal rate, $(k_1 + k_2)$, and of the calculated uptake.

After the control period, each patient was given daily a large oral dose of iodine either as a solution of potassium iodide or as Lugol's solution. Observations were continued for a period of from four to eleven days. The data are presented in Figs. 50–53 and in Table XVII.

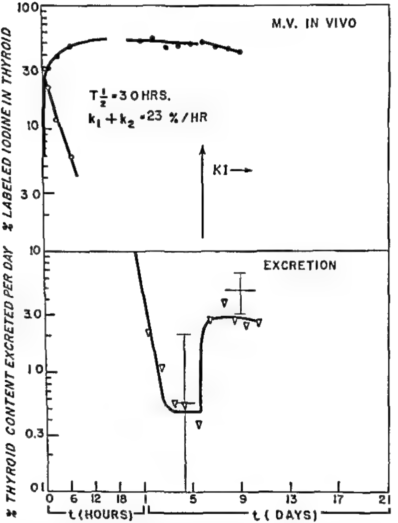

Fig. 52 The subject of this experiment was a 46-year-old female with a large nodular goiter estimated to weigh 180 gm. The construction of the chart is identical with that of Fig. 50.

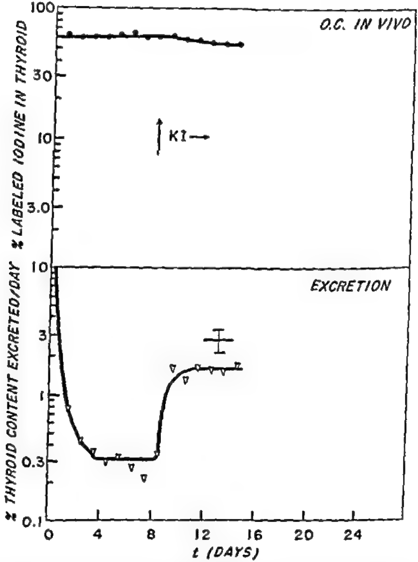

Fig. 51. The subject of this experiment was a 37-year-old clinically euthyroid female who had a gland estimated to weigh approximately 80 gm. The construction of the chart is identical with that of Fig. 50.

TABLE XVII. PARAMETERS OF THYROID FUNCTION IN FOUR PATIENTS GIVEN LARGE DOSES OF POTASSIUM IODIDE.

Patient	Serum protein-bound iodine (μg/100 ml)	Iodine excreted: control period (μg/day)	$k_1 + k_2$ (%/hour)	Calculated uptake (per cent)	Measured uptake (per cent)	Thyroid iodine content (μg)	*In vivo* half-time (days): Control period	*In vivo* half-time (days): Iodide period
D. F.	—	8 0	18	61	71.2	9650	48 5 ± 33.3	23 8 ± 2 6
O. C.	6 1	38 9	—	—	61 1	7800	− 136 ± 103	24.9 ± 4 2
M. V.	6 6	42 4	23	69	53 2	4180	138 ± 380	14 5 ± 5.5
R. M.	5 4	14 1	41	83	65 1	530	17 1 ± 2 6	8 5 ± 0 7

	In vivo release rate (%/day): Control period	*In vivo* release rate (%/day): Iodide period	Mean labeled-iodine excretion (%/day): Control period	Mean labeled-iodine excretion (%/day): Iodide period	Thyroid iodine release (μg/day): From control period	Thyroid iodine release (μg/day): From iodide period	Ratio: Iodide period / control period
D F	1 43 ± 0 98	2 91 ± 0 32	0 58	3 53	186	340	1 83
O. C.	− 0 51 ± 0 39	2.78 ± 0 47	.30	1 61	61	126	2 07
M V	0 55 ± 1 50	4.79 ± 1 82	.48	2 73	38	114	3 00
R. M.	4.05 ± 0 62	8 16 ± 0 64	2 21	17.0	69	90	1 30
						Mean	2 05

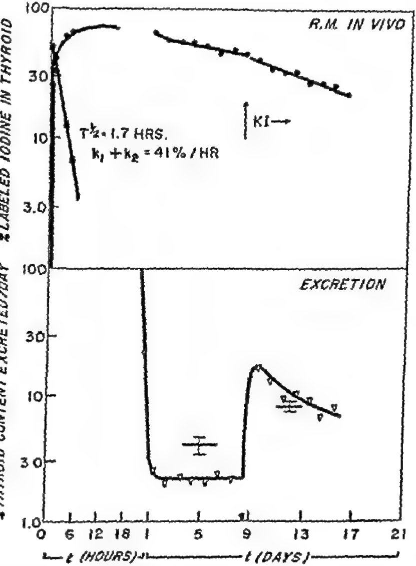

Fig 53. The subject of this experiment was a 13-year-old female with a thyroid estimated to weigh approximately 40 gm. The construction of the chart is identical with that of Fig. 50.

tion charts, the difference in excretion was of such magnitude as to make unnecessary any statistical analysis.

The excretion rates of labeled iodine are given in Table XVII. These values are the averages for the control and iodide periods in all cases except for the iodide period of R.M. The excretion curve in this patient is seen to rise rapidly to a value of about 17 per cent of the thyroid content per day and thereafter to fall off rapidly. Since this patient had the smallest thyroid iodine content, the logical explanation would seem to be a decrease in specific activity of the gland resulting from the accumulation of large amounts of unlabeled iodine. Therefore, it appeared that the maximum value might be a better estimate of the true rate of excretion during the administration of iodide. The ratio of labeled iodide excretion during iodide administration to that of the control period ranged from 5.4 to 7.7. However, from Eq. (8.29) it is seen that the increase in excretion or release rate expected from complete blocking of reutilization of iodide released by the metabolism of hormone in the extrathyroidal tissues is $1/(1 - U)$. For the four patients this ratio, which, except for patient O.C., was based upon the calculated uptake, varied from 2.1 to 5.9.

This discrepancy between expected and observed rates of release of labeled iodine after the administration of iodide can be observed more directly by calculation of the thyroid iodine release, H, during the control period and the iodide period. The calculation during the control period has been made by means of Eq. (4.4), and that during the iodide period by means of Eq. (8 33). The values during the control period ranged from 38 μg per day to 186 μg per day, whereas during the iodide period the values ranged from 90 to 340 μg per day. The ratios of thyroid iodine release during the iodide period to that of the control period ranged from 1.30 to 3.00 with a mean of 2.05. It is interesting that the smallest ratio, 1.30, was obtained from patient R.M. The fall in urinary

The retention and excretion curves of Figs. 50–53 are plotted in the same manner as those of the control patients of Chapter 9. The beginning of the administration of iodide is indicated by the arrow. The excretion data are plotted in per cent of the thyroid content excreted per day on the second time scale. The rate constant of release from the thyroid together with its standard error is plotted for comparison on the excretion chart.

The four patients are listed in Table XVII in order of decreasing thyroid iodine content. The total disposal rates in three of the four patients were 18, 23, and 41 per cent per hour, corresponding to calculated uptakes of 61, 69, and 83 per cent. In patients D.F. and M.V., the calculated and observed uptakes agree, but in patient R.M. the calculated uptake is considerably greater than that observed. This would be expected from the small thyroid iodine content of patient R.M., 530 μg (cf. Chapter 8). The expected high excretion rate of labeled iodine for this patient was also observed.

The values of thyroid iodine were calculated by means of Eq. (8.21), using the iodide and labeled iodide excretion of the control period and the observed uptake. The protein-bound iodine concentration in the three patients in whom it was observed was normal.

The *in vivo* release rate and corresponding half-times were calculated from the exponential portions of the control and iodide periods of the retention curves of Figs. 50–53 by the method of least squares. These are shown with their standard errors in Table XVII. The errors in the release rates and half-times during the control periods are large because the rates are small and because the control periods were short. The rates during the iodide period were sufficiently large so that the differences were greater than two standard errors in all cases except that of D.F., where it was greater than one standard error of the difference. As seen from the excre-

also by preventing the reutilization of iodide released within the thyroid gland itself by the enzymatic deiodination of iodinated tyrosine. However, most, if not all, of the effects of iodide can be attributed to dilution of labeled iodine. In the presence of a high concentration of iodide the probability would be very small that a given atom of radioactive iodine released by the deiodination of iodinated tyrosine would reënter the synthetic cycle. Conversely, the probability would be very large that it would diffuse out into the blood and be excreted in the urine. Thus, so far as the fate of labeled iodine stored in the thyroid is concerned, the initial effect of large doses of iodide should be very much like the effect of methimazole, though somewhat complicated by the decrease in specific activity that would occur as the thyroid gland replenished its stores of hormone.

Means and Lerman [5] in 1939 postulated that the therapeutic effect of iodide was to inhibit the release of hormone from the hyperplastic gland of Graves' disease. The rapid improvement that occurs when patients with Graves' disease are treated with iodide can hardly be due to anything but a decrease in rate of secretion of hormone. The four patients studied here showed a definite and clear *increase* of rate of loss of iodine from the gland during administration of iodide. However, it cannot definitely be stated that hormone secretion was not diminished because the iodide release might have masked this effect.

Recently Goldsmith [3], in experiments similar in design to those of this study, showed an *upward* deflection of the *in vivo* retention curve when large doses of iodide were given to patients with hyperthyroidism. Adams and Purves [1] have observed the same phenomenon in a thyrotoxic subject, and Ansell and Miller [2] observed no change of slope of the retention curve during administration of iodide to their thyrotoxic patients. These findings can best be interpreted as an inhibition of the release of hormone by the

excretion rate of labeled iodine after the initial peak following the start of the iodide period is evidence of decrease of specific activity in the gland during the iodide period. Since decrease of specific activity would produce an apparently low value for thyroid iodine release, it may be that the true ratio was larger than that observed.

Discussion

The effect of adding large daily doses of iodide was to increase sharply the apparent rate of release of labeled iodine from the gland. The change in *in vivo* release rate was greater than two standard errors of the difference in three patients and greater than one in one patient. The change in excretion of labeled iodine was large and abrupt. The magnitude of the change in excretion cannot be explained on the basis of *blocking of reutilization of labeled iodine released from the metabolism of hormone in the tissues*, although it has already been shown that doses of iodide of this magnitude almost completely prevent the uptake of labeled iodine.

The calculated thyroid iodine release during the iodide period is at least twice as much as that expected solely from the release of hormone. If this excess of iodine had been released as hormone, the new iodide excretion rate would not have reached its maximum for several days. Actually, the maximum value is reached in one to two days. It appears, therefore, that the extra iodide is released in a form which is rapidly excreted, presumably iodide.

The increased rate of loss of labeled iodine in these patients given large doses of iodide is strikingly similar, both qualitatively and quantitatively, to the increased loss of labeled iodine that occurred during the administration of methimazole. In the previous chapter it was postulated that methimazole increases the rate of loss of labeled iodine not only by preventing the reaccumulation of *labeled iodide* released from hormone in the extrathyroidal tissues, but

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iodine, but the possibility cannot be excluded that the slower or unchanged release rates during administration of iodide were due in part to a decrease of specific activity, a possibility entertained by Ansell and Miller. The effect of dilution of the labeled iodine of the gland by accumulation of iodine was apparent in one patient, R.M., and may have been present in the other patients. Why there is this difference between hyperthyroid patients and iodide-deficient patients is not clear.

It would appear that all estimates of hormone release after massive doses of iodide are clouded with technical and physiological uncertainties. Perhaps the most satisfactory measurement would be serial determinations of the protein-bound iodine after the administration of iodide. The technical difficulties of this determination in the presence of large quantities of iodide are great, but have now been solved [4].

Summary

1. The administration of large doses of iodide to four patients who had previously been given labeled iodide resulted in increased rates of release of labeled iodine from the glands and increased rates of excretion in the urine.

2. The release of iodine from the gland during the administration of iodide was approximately twice that observed during the control period. There is strong evidence that the extra iodine left the thyroid as iodide.

3. These data are at variance with those observed under similar circumstances in the hyperplastic gland of Graves' disease. Iodide administered to a patient with Graves' disease results in an unchanged or slower rate of release of labeled iodine.

4. The disappearance of large amounts of iodide from the gland after administration of iodide precludes any quantitative conclusions concerning the change in the rate of release of hormonal iodine.

thyroid gland with an abundance of stored hormone the rate of secretion of labeled iodine is so small that the observed uptake is very close to the theoretical uptake. However, in the patient with severe iodine depletion the normal daily secretion of hormone may represent a considerable fraction of the total store of hormone in the gland. The rate of secretion of *labeled* hormone is, therefore, very rapid, and the maximum observed uptake may be so much smaller than the theoretical uptake that it no longer indicates accurately the true avidity of the thyroid gland for iodine. Even so, among the Mendoza patients there was a good correlation between observed uptake and intake of iodine in the diet as measured by the daily urinary excretion of iodide. Thus patients who had a very low excretion of iodide had glands with high avidity for iodide as measured by the uptake, and conversely patients who had a large excretion of iodide had low uptake.

From values for uptake and excretion of iodide, it is possible to calculate the rate at which thyroid hormone is being secreted. This rate for the Mendoza subjects proved to be similar to rates estimated for euthyroid subjects in areas of iodine abundance. Patients whose uptakes were high tended to have a slightly lower concentration of protein-bound iodine in the serum than did patients whose uptakes were low or normal.

The adjustments that occurred when iodine-deficient patients were given daily oral doses of iodide were seen to occur quite slowly. It was possible to calculate the rates at which these patients were retaining the supplementary iodide and to estimate the net gain in iodine that might have occurred when the patients had returned to a new equilibrium state. The net retention was surprisingly high and was correlated with the size of the supplement. Patients who were given larger supplements retained more iodine than did patients who were given smaller ones. One of the patients

12

RECAPITULATION AND SUGGESTED STUDIES

In this monograph we have been concerned with iodine metabolism as disclosed by a study of a group of subjects *many of whom were subsisting on a diet that was inadequate* in iodine. Our patients had made certain adjustments of adaptation to iodine deficiency whereby they were able to maintain themselves in a normal state of health, but at the expense of enlargement of the thyroid gland. Against this background of minimal iodine intake, it was possible to observe the patterns of iodine metabolism and the changes imposed by the deficiency. In addition, it was possible to unmask certain of the dynamics of iodine transfer through various metabolic stages within the body.

The iodine-deficient thyroid gland clears iodide from the blood more rapidly than does the gland of the patient supplied with an abundance of iodine. This increased clearance is reflected by the increased rate at which labeled iodide is accumulated by the thyroid, and by a correspondingly increased *theoretical* uptake, which is the portion of the available iodide used by the thyroid gland. Usually, it is also reflected by a higher *observed* uptake of labeled iodide. However, it must be borne in mind that the observed uptake is the net result of the accumulation of labeled iodide and the simultaneous secretion of a portion of the labeled iodine which has been synthesized into hormone. In the normal

thyroid gland with an abundance of stored hormone the rate of secretion of labeled iodine is so small that the observed uptake is very close to the theoretical uptake. However, *in the patient with severe iodine depletion the normal* daily secretion of hormone may represent a considerable fraction of the total store of hormone in the gland. The rate of secretion of *labeled* hormone is, therefore, very rapid, and the maximum observed uptake may be so much smaller than the theoretical uptake that it no longer indicates accurately the true avidity of the thyroid gland for iodine. Even so, among the Mendoza patients there was a good correlation between observed uptake and intake of iodine in the diet as measured by the daily urinary excretion of iodide. Thus patients who had a very low excretion of iodide had glands with high avidity for iodide as measured by the uptake, and conversely patients who had a large excretion of iodide had low uptake.

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The adjustments that occurred when iodine-deficient patients were given daily oral doses of iodide were seen to occur quite slowly. It was possible to calculate the rates at which these patients were retaining the supplementary iodide and to estimate the net gain in iodine that might have occurred when the patients had returned to a new equilibrium state. The net retention was surprisingly high and was correlated with the size of the supplement. Patients who were given larger supplements retained more iodine than did patients who were given smaller ones. One of the patients

who was given 1500 μg of iodide daily developed thyrotoxicosis. When single graded doses of iodide were given along with tracer doses of labeled iodide, the portion of the supplement that was accumulated in the thyroid was independent of the administered dose up to approximately 1 mg, but above this a decreasing fraction of the dose was taken up by the thyroid. It appears, therefore, that the iodide-deficient thyroid gland adjusts to an increase in iodide supply by a slow return to a new equilibrium state, and that in the process a considerable amount of iodine is stored against future needs.

The thyroid gland of the iodine-deficient patient is presumably under stimulation by the thyrotropic hormone of the anterior pituitary gland. It can be put at rest by the administration of daily doses of desiccated thyroid. The adjustments are slow and are incomplete after two weeks, but the dosages required are of the same order of magnitude as those required for euthyroid subjects in iodide-sufficient areas.

The kidney plays no role in adaptation to iodine deficiency. A study of renal clearance of several patients who were manifestly deficient in iodine revealed renal iodide clearances within the limits of normal. The adaptation seems to be entirely dependent upon the thyroid. The adjustment to iodine deficiency is an expansion of the capacity of the thyroid to remove iodide from the blood. Thus the rate constant of renal removal of iodide from the blood is normal, but for the thyroid it is many times normal.

From measurements of uptake, of the amount of labeled iodine remaining in the gland, and of excretion of iodide and of labeled iodide, it is possible to calculate the amount of iodine in the thyroid gland. This quantity was found to vary surprisingly from patient to patient.

The rate at which labeled iodine disappears from the thyroid is a complex function and is dependent upon several

factors, among them the quantity of iodine in the gland. Theoretically, the disappearance curve is always biphasic, there being a more rapid initial phase as labeled iodine is secreted and before labeled hormone is metabolized in the periphery to release labeled iodide for reutilization by the gland. The second phase is a simple exponential function. In the thyroid gland containing an abundance of iodine the first phase is not easily observed, but those patients whose thyroid glands contained an extremely small amount of iodine demonstrated a very sharp initial fall in the thyroid content of labeled iodide during the first two or three days, and then a change to an exponential and slower rate of loss. By means of an analogue computer an attempt was made to show that the biphasic nature of the disappearance curve of labeled iodine from these thyroid glands could be accounted for in the manner already described, assuming that the labeled iodine of the gland occupied a single compartment with a single release rate. It was found, however, that there were gross discrepancies between the simple three-compartment model and the observed facts. When it was postulated that the initial rapid fall of the curve was due not only to a delay in availability of iodide for reutilization, but also to the presence in the thyroid gland of two compartments with different rates of turnover, one rapid and one slow, then a good correlation could be found between observations and the behavior of labeled iodine predicted from such a four-compartment model. Under conditions of extreme iodine want, therefore, where the iodine stores in the thyroid have been almost exhausted, a rapid secretory phase may be observed, which may be direct secretion of hormone into the blood from the parenchymal cells, and a slower phase, which may be due to secretion from colloid stores, and which usually dominates the observations in glands less depleted of iodine.

When labeled iodine was given and allowed to accumulate

in the gland, and when its disappearance rate had been established, the administration of a drug such as methimazole caused an increase in the rate of loss of labeled iodine from the gland. This rate of loss was in excess of that which could be accounted for by simple inhibition of reutilization of iodide made available from peripheral breakdown of labeled hormone. Probably this iodide came from deiodination of mono- and diiodotyrosine in the gland by Roche's deiodinase.

The physiological behavior of the iodine-deficient gland is consistent with current theory that the gland is under the control of the thyrotropic hormone of the anterior pituitary gland. However, these patients were responsive to additional thyrotropic hormone. When the rate of disappearance under methimazole medication had been established, the administration of thyrotropic hormone resulted in an increase in the rate at which iodine was lost from the gland and appeared in the urine. Thus, although these glands were under increased stimulation from thyrotropic hormone, they were not under maximal stimulation.

When large daily doses of iodide were given to patients who had previously received labeled iodide, there was an increase in the rate at which the labeled iodide was lost from the gland. The explanation of this increased rate of loss is very likely analogous to the explanation offered above for the similar loss of iodine during the administration of methimazole. Studies by others have shown an unchanged or decreased rate of loss of labeled iodide from the gland when therapeutic doses of potassium iodide or of Lugol's solution have been given to the subject with Graves' disease. The cause of the differences between the hyperplastic gland of Graves' disease and that of iodine deficiency is not apparent.

It was inevitable that many possibilities for further study became apparent as our data unfolded and as we attempted

to fit them into hypotheses. We should now like to share these thoughts with the reader in the hope that our experiences may act as stimuli to further research.

Iodine and the Etiology of Goiter

Any remaining doubt that iodide deficiency can be a cause of endemic goiter has been erased by the present studies. This is not to say that iodide deficiency is the cause of all endemic goiter, for it is quite possible that unrecognized goitrogenic substances may cause goiter by creating a block of utilization of iodide for hormone production.

The most direct way to settle the problem of the role of iodide deficiency in a field study of a particular endemic is to measure the content of iodide in 24-hour collections of urine from fair samples of the population under scrutiny. If facilities are available, the survey can be further embellished by measurements of the uptake of labeled iodine. It is to be hoped that the endless controversies over the etiology of endemic goiter might be brought to a close by this kind of documentation.

Serum Hormonal Iodine and Goiter

The Mendoza patients presented few, if any, of the overt clinical features of hypothyroidism, and only a very few had serum protein-bound iodine concentrations that were below the generally accepted normal range. Nevertheless, it was possible to show an inverse relation between avidity of the thyroid for iodide and the protein-bound iodine. It would be of interest to extend this relation into the hypothyroid range in regions where the severity of the endemic is such that many of the goitrous members of the population are distinctly hypothyroid or even myxedematous. If, in addition, data on iodide excretion were available, it should be possible to calculate the daily secretion rates of hormone and, with a wide range of values, to show the expected relation

between the rate of hormonal iodine secretion and the concentration of hormonal iodine in the serum, a relation which was not apparent from our observations.

Studies with Iodide Supplements

The studies in which iodide was given to patients in small daily supplements were necessarily incomplete. The disclosure that their total net retention of iodine was not leading them back toward some hypothetical "normal" quantity of iodine in their glands, but rather that the retention was dependent upon the size of the supplement, is of considerable theoretical as well as practical interest. The experiment is in need of repetition where the observations can be continued until a new equilibrium state is reached after the old one is upset by increasing the daily iodine intake.

The experiment should be repeated often enough, and with a sufficient number of different doses, so as to define the conditions most likely to produce jodbasedow, a phenomenon which apparently occurred in one of our Mendoza patients.

Of course, one should not overlook the very attractive possibility of confirming theoretical calculations by first estimating the quantity of iodine in the gland, then noting the net positive balance of iodine for several weeks, and finally assaying the quantity of iodine in the gland by direct chemical measurement after surgical excision. Perhaps this is too much to hope for.

Dynamic State and the Model

At the time our observations were made, it was not practical to measure accurately the blood concentrations of labeled iodide after routine tracer doses. With the improved well-type scintillation crystal counters now available, it should be possible to observe with considerable accuracy the fluctuations in the labeled iodine of the blood. These measure-

ments would be invaluable in further study of the biphasic *in vivo* retention curves of patients with small thyroid iodine contents. Thus it could possibly be shown that concomitant with the rapid fall in labeled iodine in the gland there is a rapid rise in the protein-bound labeled iodine of the plasma, and that it reaches a very high specific activity. Both the concentration of labeled iodine and the specific activity might then level off and decline during the second and less precipitous phase of the *in vivo* decay curve. These observations would be further evidence that the organic iodide of the thyroid pool is composed of two compartments which have differing dimensions and rate constants. The rate constant of the compartment with the more rapid turnover could be calculated with fair accuracy from blood data, whereas it can only be approximated from the presently available *in vivo* data.

The Quantity of Iodine in the Thyroid Gland

It has already been mentioned that one of the most puzzling and challenging observations of the entire study was the extraordinary variability in the quantity of iodine sequestered within the glands of these patients It was observed in Chapter 10 that the absolute secretion rate of hormone was independent of gland content, but that the percentage of the gland content secreted per day was correlated inversely with the gland content of iodine. Further, thyrotropin in the dose given seemed very nearly to double the proportion of gland content secreted per day independently of the total quantity of stored iodine. It has been shown in Chapter 5 that iodide supply plays a major role in determining the quantity of reservoir iodine in the gland. The quantity of stored hormonal iodine, Q_G, therefore must be the resultant of a number of factors, of which thyrotropin secretion rate and iodine supply are among the most important. One possible experimental approach to the problem would be

along the lines of the iodine supplement study described earlier. One could measure Q_O, uptake, U, net release rate, k_4', and hormonal iodine secretion rate, H, before adding the supplementary iodide, and remeasure the same parameters after the new equilibrium state had been attained. In this way the regulating effect of dietary iodide on gland content and function could be observed.

The Meaning of Uptake

Conventionally, uptake of labeled iodine is defined as that fraction of the tracer dose which is present in the thyroid gland at an arbitrary time after administration. This time is usually chosen to be 24 or 48 hours. It quickly becomes apparent that such a definition is inadequate when one is dealing with patients who may be secreting part of the labeled iodine as hormone before the maximal extraction from the blood has been achieved. Thus the measurement fails to account for some of the administered labeled iodine that passed through the gland. One technique for circumventing this difficulty is to extrapolate the downward slope of the retention curve back to zero time, but this is obviously inaccurate if the decay curve is biphasic, as some of them were. It appears, therefore, that the conventional use of the term "uptake" has limited meaning when one is dealing with patients whose thyroid glands have very high avidity for and rapid turnover of iodide.

A far better method of measuring avidity — and this is the goal of all uptake tests — would be one that gave k_1, the percentage of the iodide compartment which is cleared of iodide by the thyroid gland in unit time. Wide variations in k_1 would doubtless be encountered among patients who had observed uptakes that were not appreciably different.

The problem, then, is that of determining k_1. Perhaps the most accurate method would be from simultaneous measurements of blood and urine collected during short periods after

an intravenous dose of labeled iodine has attained uniform distribution throughout the iodide space. The blood concentration when plotted on a semilogarithmic scale gives the total disposal rate, $(k_1 + k_2)$. The simultaneously observed renal disposal rate is k_2. Then k_1 is derived by difference. Practically, k_1 for iodide-deficient patients is large with respect to k_2, and k_2 can be assumed to be 7 per cent per hour, unless there is evidence of renal damage. The rate k_1 can also be derived from the *in vivo* curve as has already been shown, but this method is probably less accurate than that of measuring the blood.

It would obviously be of great value to resurvey a group of patients with endemic goiter due to iodine deficiency, relating the quantity of iodide in the gland, Q_G, protein-bound iodine, hormone secretion rate, H, urinary excretion rate, E, and net thyroid release rate, k_4', to the thyroid disposal rate, k_1, rather than to uptake. Such a study would be exceedingly laborious, but it would be much more precise than the present studies.

The Effects of Iodide and Methimazole

Large doses of iodide and of methimazole were observed to effect the release of more than twice the amount of iodide that would be expected from the simple inhibition of uptake.

Two possibly fruitful lines of further investigation can be suggested. Blood measurements of labeled iodine and iodide before and after methimazole block should provide a clue to whether the excess iodine is inorganic iodide or hormonal iodine, although the rapid appearance in the urine strongly suggests that it is not bound to protein. The same experiment could be done, substituting perchlorate for iodide or methimazole. Perchlorate inhibits the trapping of iodide by the gland. This substance has a different mode of action from iodide, which simply dilutes out the labeled iodide, or methimazole, which prevents organic incorporation of

trapped iodide. Therefore, perchlorate might fail to effect the release of more iodide than accountable to inhibition of uptake.

Histology and Oncology

There was no opportunity to correlate physiological observations with anatomical and microscopic findings. One might have expected hyperplasia and colloid involution as has previously been described in endemic goiter [1, 2]. In addition, cyst formation, fibrous replacement, and various types of nodules would have been expected in the older patients.

Application of the techniques of radioautography in a study of patients with endemic goiter would seem to offer an unusually promising approach to the investigation of the pathogenesis of tumors of the thyroid gland. Taylor [3, 4] has already described his findings in sporadic goiter in England. It has commonly been observed, as it was in the Mendoza patients, that the diffuse enlargement of the thyroid glands of young patients with endemic goiter gives way to nodular goiter in older patients. Radioautography should show the functional and anatomical changes that occur as the gland passes from a state of diffuse hyperplasia to one where the hyperplasia is focal and where hyperplastic and involutionary nodules occur.

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APPENDIX A

GLOSSARY

Balance: The net increment or decrement in the iodine content of a compartment or of the body as a whole. This is usually expressed in micrograms per day.

Blocking agent: As employed here, any of the thioamide drugs which prevent the chemical combination of trapped iodide with tyrosyl groups within the thyroid gland.

Clearance: The virtual volume of plasma from which a substance is completely extracted by an organ in unit time. It is usually expressed in milliliters per minute

Compartment: In general terms, any experimentally identifiable portion of the total body content of the material being studied; as used in this monograph, any subdivision of total body iodine which, during tracer experiments, behaves *as if* it were homogeneous, that is, becomes uniformly labeled when a tracer has been added to it and sufficient time has been allowed for distribution. Compartments are postulated only when they can be clearly identified experimentally. Identification may depend upon the chemical state of the iodine, upon its anatomical location, or upon both. For example, the organic iodine in the thyroid gland, though actually present in at least four different amino acids, is usually ascribed to a single compartment because the individual components cannot be distinguished experimentally *in vivo*, and because, shortly after uptake of labeled iodine by the thyroid is complete, the organic iodine in the gland usually behaves as if it is uniformly labeled.

Disposal rate: The fraction of the substance in a compart-

trapped iodide. Therefore, perchlorate might fail to effect the release of more iodide than accountable to inhibition of uptake.

Histology and Oncology

There was no opportunity to correlate physiological observations with anatomical and microscopic findings. One might have expected hyperplasia and colloid involution as has previously been described in endemic goiter [1, 2]. In addition, cyst formation, fibrous replacement, and various types of nodules would have been expected in the older patients.

Application of the techniques of radioautography in a study of patients with endemic goiter would seem to offer an unusually promising approach to the investigation of the pathogenesis of tumors of the thyroid gland. Taylor [3, 4] has already described his findings in sporadic goiter in England. It has commonly been observed, as it was in the Mendoza patients, that the diffuse enlargement of the thyroid glands of young patients with endemic goiter gives way to nodular goiter in older patients. Radioautography should show the functional and anatomical changes that occur as the gland passes from a state of diffuse hyperplasia to one where the hyperplasia is focal and where hyperplastic and involutionary nodules occur.

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Serum protein-bound iodine: The iodine of the serum which is precipitable by the usual protein precipitants, and which is nondialyzable. Normally, it consists chiefly of thyroxine and triiodothyronine iodine but it may include other noncalorigenic compounds of iodine derived from iodine-containing drugs.

Specific activity: The ratio of labeled-iodine content to the iodine content of any compartment. The term is also applied to the ratio of labeled iodide to iodide in the urine.

Uptake: The fraction of iodide in the iodide compartment entering the thyroid gland. Estimates of this quantity may be obtained from the labeled-iodide disposal rates or from observations of thyroid content of labeled iodine at an arbitrary time after administration. The *observed uptake* is customarily determined by measurements of thyroid content at 24 or 48 hours, and is subject to the systematic error that when the measurement is made some of the accumulated labeled iodine may have left the gland. The *calculated uptake,* obtained from disposal rates, is subject to certain technical errors which are discussed in the text.

ment that enters another compartment or is excreted in unit time. For example, k_2 is the renal disposal rate of iodide in per cent of the total iodide of the iodide compartment excreted per hour in the urine.

Endemic goiter: Goitrousness which is particularly prevalent in a geographically definable area.

Half-time or half-period: The time required for the labeled-iodine content of a compartment to decrease by one-half.

Labeled iodine: A hypothetical quantity of iodine administered with and measured by means of radioactive iodine. This quantity is always expressed as a fraction, and does not involve physical decay of the radioactive iodine. Confusion may arise when one speaks of the *specific activity* of labeled *iodine in a compartment. By this term is meant the ratio of* the fraction of the initially administered tracer dose present in the compartment to the total iodine in the compartment at that time. The assay of the quantity of labeled iodine is by detection of radiation, but since the radioiodine that marks the tracer is decaying at the same rate as the standard to which it is compared, the physical decay is eliminated, and the resulting value is a true measure of the fraction of the initial dose present in the assay sample at time t.

Mendoza: A province of western Argentina; also, the capital city of that province.

Recovery: The sum of the observed uptake of labeled iodide by the thyroid and the iodide that has been excreted during the first 48 hours after administration of a tracer dose.

Retention curve: The curve of labeled iodine in the thyroid plotted against time.

Secular equilibrium: The condition existing in a multicompartmental system when the ratio of specific activities in any two specified compartments approaches asymtotically a constant value. This is in contrast to *ideal equilibrium,* which in general exists only instantaneously, and is characterized by equal specific activities.

as the rate constant for loss of labeled iodine from the thyroid; and (3) there is no excretion of organic iodine ($k_5 = 0$). It is obvious that these assumptions are not entirely compatible, but in those cases where it is impossible to distinguish from the experimental data the two slopes, k_4 and k_4' (that is, when k_4 is small), an approximate description of the system can be given.

With these assumptions, Eq. (8.6) reduces to

$$Q_B \frac{dS_B}{dt} = k_4 Q_G S_G - k_6 Q_B S_B \tag{B.1}$$

and Eq. (8.5) becomes

$$Q_G \frac{dS_G}{dt} = -k_4' Q_G S_G, \tag{B.2}$$

which upon integration becomes

$$Q_G S_G = U e^{-k_4' t}. \tag{B.3}$$

It will be assumed that the solution for $Q_B S_B$ in Eq. (B.1) contains terms with the two exponentials, $e^{-k_4' t}$ and $e^{-k_6 t}$:

$$Q_B S_B = U(h_a e^{-k_4' t} + h_b e^{-k_6 t}), \tag{B.4}$$

where h_a and h_b are constants of integration. The differential of this quantity is

$$Q_B \frac{dS_B}{dt} = U(-h_a k_4' e^{-k_4' t} - k_6 h_b e^{-k_6 t}). \tag{B.5}$$

Introducing Eqs (B 3), (B.4), and (B.5) into Eq. (B.1) and collecting terms, one finds

$$[h_a(k_6 - k_4') - k_4] e^{-k_4' t} = 0. \tag{B.6}$$

For the assumed expression, Eq. (B.4), to be valid for all values of time, the term in brackets must equal zero. This yields

$$h_a = \frac{k_4}{k_6 - k_4'}. \tag{B.7}$$

APPENDIX B

APPROXIMATE SOLUTIONS FOR THE DIFFERENTIAL EQUATIONS OF THE THREE-COMPARTMENT MODEL

The differential equations for the three-compartment model are given in Chapter 8:

$$Q_I \frac{dS_I}{dt} = k_6 Q_B S_B - (k_1 + k_2) Q_I S_I, \tag{8.4}$$

$$Q_G \frac{dS_G}{dt} = k_1 Q_I S_I - k_4 Q_G S_G, \tag{8.5}$$

$$Q_B \frac{dS_B}{dt} = k_4 Q_G S_G - (k_5 + k_6) Q_B S_B. \tag{8.6}$$

If only short time intervals are considered, approximate solutions for iodide metabolism may be readily obtained as discussed in Chapter 8 However, the description of events following this initial uptake requires further simplifying assumptions. It is obvious from Fig. 24 that if the pathway from the iodide compartment to the thyroid were removed ($k_1 = 0$), the system would be analogous to that of series radioactive decay, which is well treated in the literature [1, 2]. The assumptions will then be made that (1) the thyroid specific activity has the initial value U/Q_G and *decays* at the single rate k_4', although the thyroid *secretes* hormone at the rate k_4; (2) transfer of iodide from the iodide compartment to the thyroid does not occur ($k_1 = 0$), except in so far as such transfer is implied by using k_4' instead of k_4

as the rate constant for loss of labeled iodine from the thyroid; and (3) there is no excretion of organic iodine ($k_6 = 0$). It is obvious that these assumptions are not entirely compatible, but in those cases where it is impossible to distinguish from the experimental data the two slopes, k_4 and k_4' (that is, when k_4 is small), an approximate description of the system can be given.

With these assumptions, Eq. (8 6) reduces to

$$Q_B \frac{dS_B}{dt} = k_4 Q_G S_G - k_6 Q_B S_B \tag{B.1}$$

and Eq. (8.5) becomes

$$Q_G \frac{dS_G}{dt} = - k_4' Q_G S_G, \tag{B.2}$$

which upon integration becomes

$$Q_G S_G = U e^{-k_4' t}. \tag{B 3}$$

It will be assumed that the solution for $Q_B S_B$ in Eq. (B.1) contains terms with the two exponentials, $e^{-k_4' t}$ and $e^{-k_6 t}$:

$$Q_B S_B = U(h_a e^{-k_4' t} + h_b e^{-k_6 t}), \tag{B.4}$$

where h_a and h_b are constants of integration. The differential of this quantity is

$$Q_B \frac{dS_B}{dt} = U(-h_a k_4' e^{-k_4' t} - k_6 h_b e^{-k_6 t}). \tag{B.5}$$

Introducing Eqs. (B.3), (B.4), and (B 5) into Eq. (B.1) and collecting terms, one finds

$$[h_a(k_6 - k_4') - k_4] e^{-k_4' t} = 0. \tag{B.6}$$

For the assumed expression, Eq. (B.4), to be valid for all values of time, the term in brackets must equal zero. This yields

$$h_a = \frac{k_4}{k_6 - k_4'}. \tag{B.7}$$

It is obvious that S_B must equal zero at time zero. From Eq. (B.4), this yields

$$h_b = -h_a. \tag{B.8}$$

Introducing Eq. (B.7) and (B.8) into Eq. (B.4) and solving for S_B yields

$$S_B = \frac{U}{Q_B}\frac{k_4}{k_6 - k_4'}\,e^{-k_4't}[1 - e^{-(k_6-k_4')t}]. \tag{B.9}$$

The specific activity of the extrathyroidal hormonal iodine rises initially with the rate constant $(k_6 - k_4')$, which is very nearly equal to k_6 since k_4' is small. It then assumes the same rate of fall as the thyroid, k_4'.

The ratio of S_B to S_G can be obtained from Eqs. (B.3) and (B.9):

$$\frac{S_B}{S_G} = \frac{Q_G}{Q_B}\frac{k_4}{k_6 - k_4'}[1 - e^{-(k_6-k_4')t}]. \tag{B.10}$$

Under the present assumptions, the total amount of iodine leaving the thyroid per day, k_4Q_G, must equal the amount of hormonal iodine reduced to iodide per day, k_6Q_B. Therefore

$$\frac{Q_G}{Q_B} = \frac{k_6}{k_4}. \tag{B.11}$$

introducing Eq. (B.11) into Eq. (B.10) and simplifying, one finds

$$\frac{S_B}{S_G} = \frac{1}{(1 - k_4'/k_6)}[1 - e^{-(k_6-k_4')t}]. \tag{B.12}$$

As this derivation is valid only when k_4 and k_4' are small compared with k_6, the following approximation is valid:

$$\frac{1}{1 - k_4'/k_6} \simeq 1 + \frac{k_4'}{k_6}, \tag{B.13}$$

and

$$\frac{S_B}{S_G} = \left(1 + \frac{k_4'}{k_6}\right)[1 - e^{-(k_6-k_4')t}]. \tag{B.14}$$

The relation between k_4 and k_4' may now be derived. The net loss of labeled iodine from the thyroid, $k_4'Q_GS_G$, is equal to the true loss, $k_4Q_GS_G$, less that reutilized from hormone breakdown, $Uk_6Q_BS_B$, or

$$k_4'Q_GS_G = k_4Q_GS_G - Uk_6Q_BS_B, \tag{B.15}$$

and

$$k_4' = k_4 - Uk_6\frac{Q_BS_B}{Q_GS_G}. \tag{B.16}$$

At times that are large compared with $1/k_6$, the second term in brackets in Eq. (B.10) becomes unity and

$$\frac{S_B}{S_G} = \left(1 + \frac{k_4'}{k_6}\right) \tag{B.17}$$

Substituting Eqs. (B.11) and (B.17) into Eq. (B.16), we obtain the following relation:

$$k_4' = k_4\left[1 - \left(1 + \frac{k_4'}{k_6}\right)U\right], \tag{B.18}$$

which reduces to

$$k_4' = k_4(1 - U) \tag{B.19}$$

when k_4' is small compared with k_6.

To derive Eq. (8.17), it is necessary to assume that the turnover of the iodide compartment is rapid compared with that of the hormonal-iodine compartment. If it were not for the constant influx of unlabeled dietary iodide, the specific activity of the iodide compartment following the introduction of the labeled iodide would rapidly approach that of the hormonal iodine. However, the dietary intake reduces the iodide specific activity and causes it to maintain a constant ratio to that of the hormonal iodine. This ratio may be determined as follows:

$$\frac{Q_I^*}{Q_I} = \frac{k_6Q_B^* + In^*}{k_6Q_B + In}; \tag{B.20}$$

In^* is, of course, zero following the introduction of labeled iodine.

The term k_6Q_B represents the amount of hormonal iodine degraded to iodide per day and therefore is equal to the amount of iodine released by the thyroid per day, H. Under the present assumptions, In equals the urinary excretion of iodide, E. An expression relating H and E has previously been derived; in terms of the present symbols it is

$$k_6Q_B = In\,\frac{U}{1-U}. \tag{B.21}$$

When this is introduced into Eq. (B.20), the latter becomes

$$\frac{Q_I^*}{Q_I} = \frac{k_6Q_B^*}{k_6Q_B + k_6Q_B(1-U)/U}. \tag{B.22}$$

Simplified, and expressed in terms of specific activity, the expression stated in Eq. (8.17) is found.

$$S_I = US_B. \tag{B.23}$$

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In^* is, of course, zero following the introduction of labeled iodine.

The term k_6Q_B represents the amount of hormonal iodine degraded to iodide per day and therefore is equal to the amount of iodine released by the thyroid per day, H. Under the present assumptions, In equals the urinary excretion of iodide, E. An expression relating H and E has previously been derived; in terms of the present symbols it is

$$k_6Q_B = In\frac{U}{1-U}. \tag{B.21}$$

When this is introduced into Eq. (B.20), the latter becomes

$$\frac{Q_I^*}{Q_I} = \frac{k_6Q_B^*}{k_6Q_B + k_6Q_B(1-U)/U}. \tag{B.22}$$

Simplified, and expressed in terms of specific activity, the expression stated in Eq. (8.17) is found.

$$S_I = US_B. \tag{B.23}$$

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